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VOLUME XXXVII

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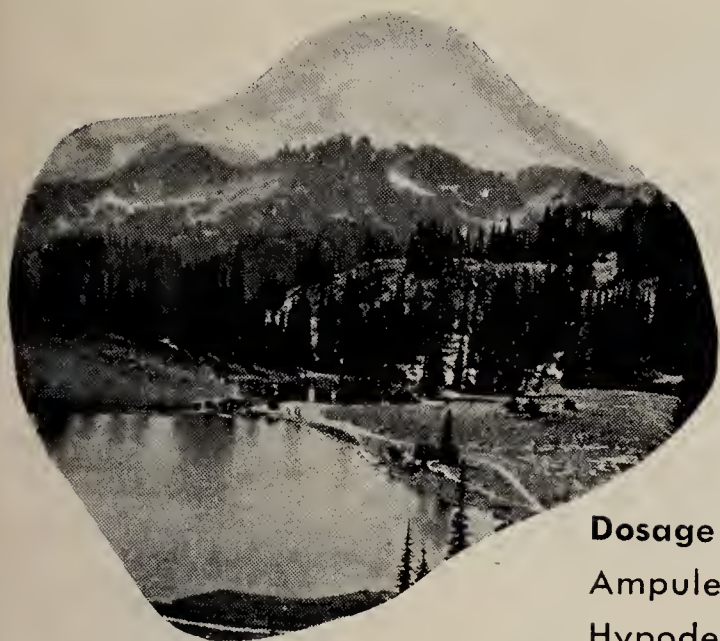
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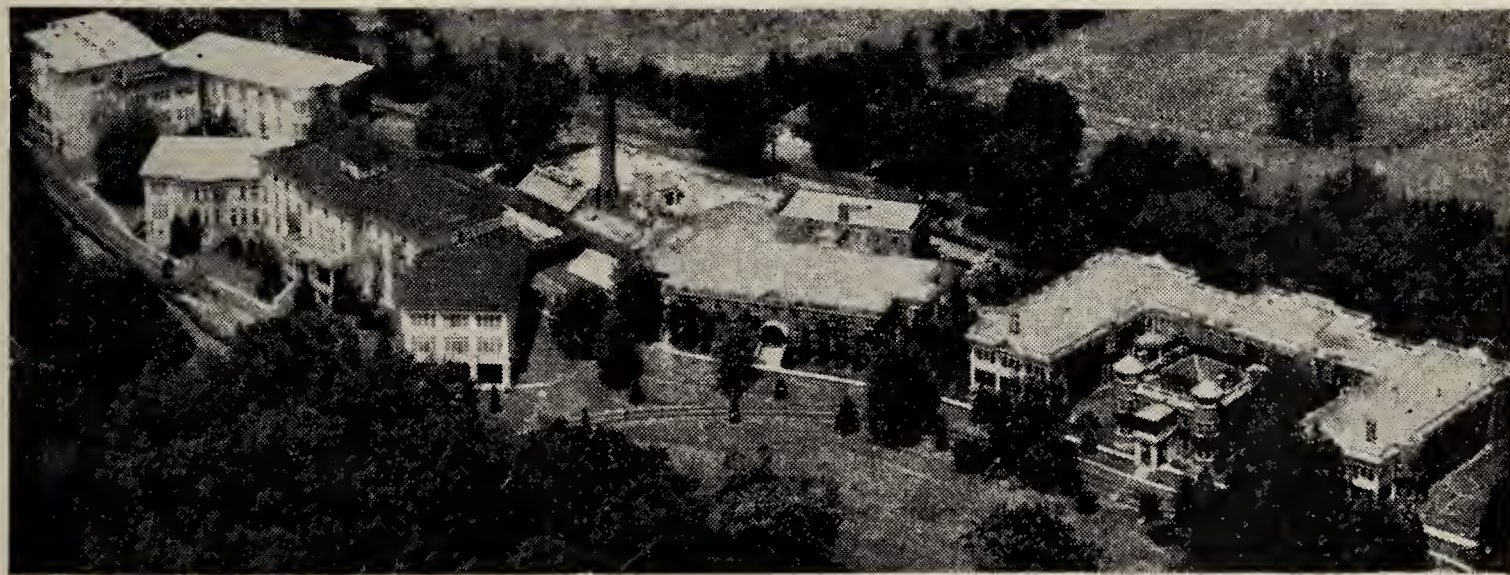
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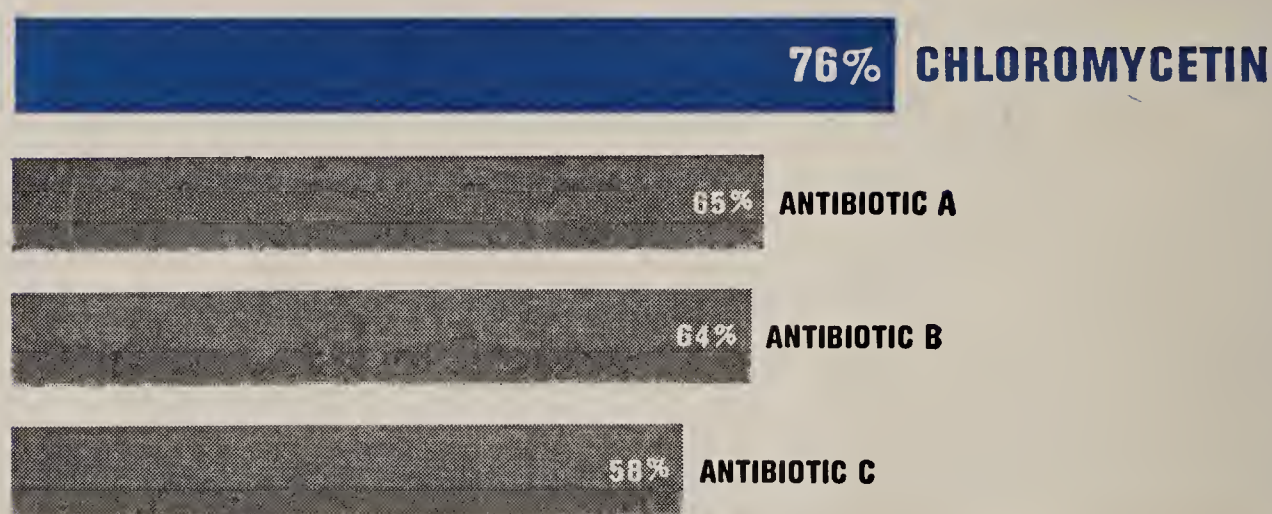
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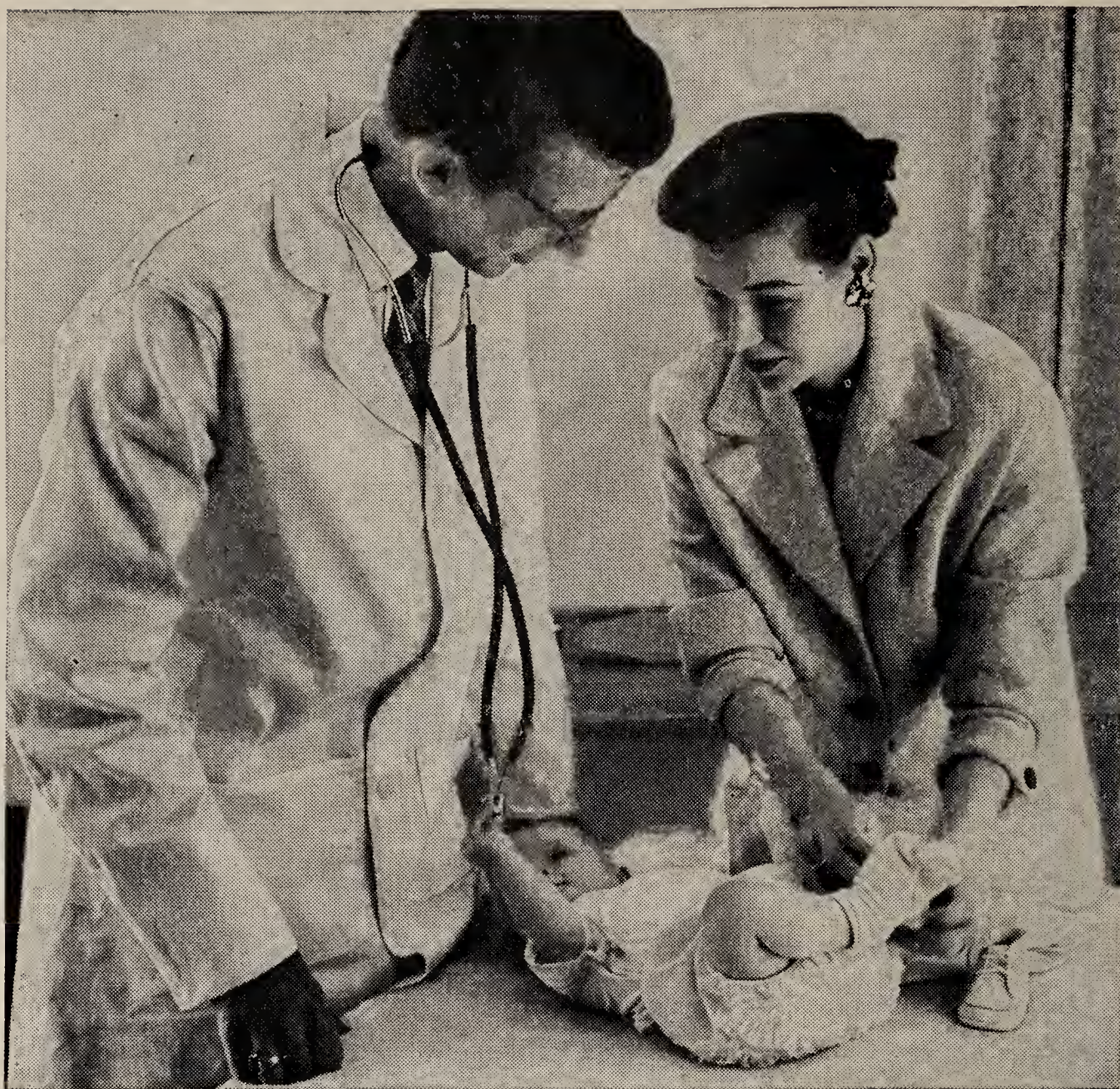
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(1) Ford, R. V., Amer. Heart J. (In Press).
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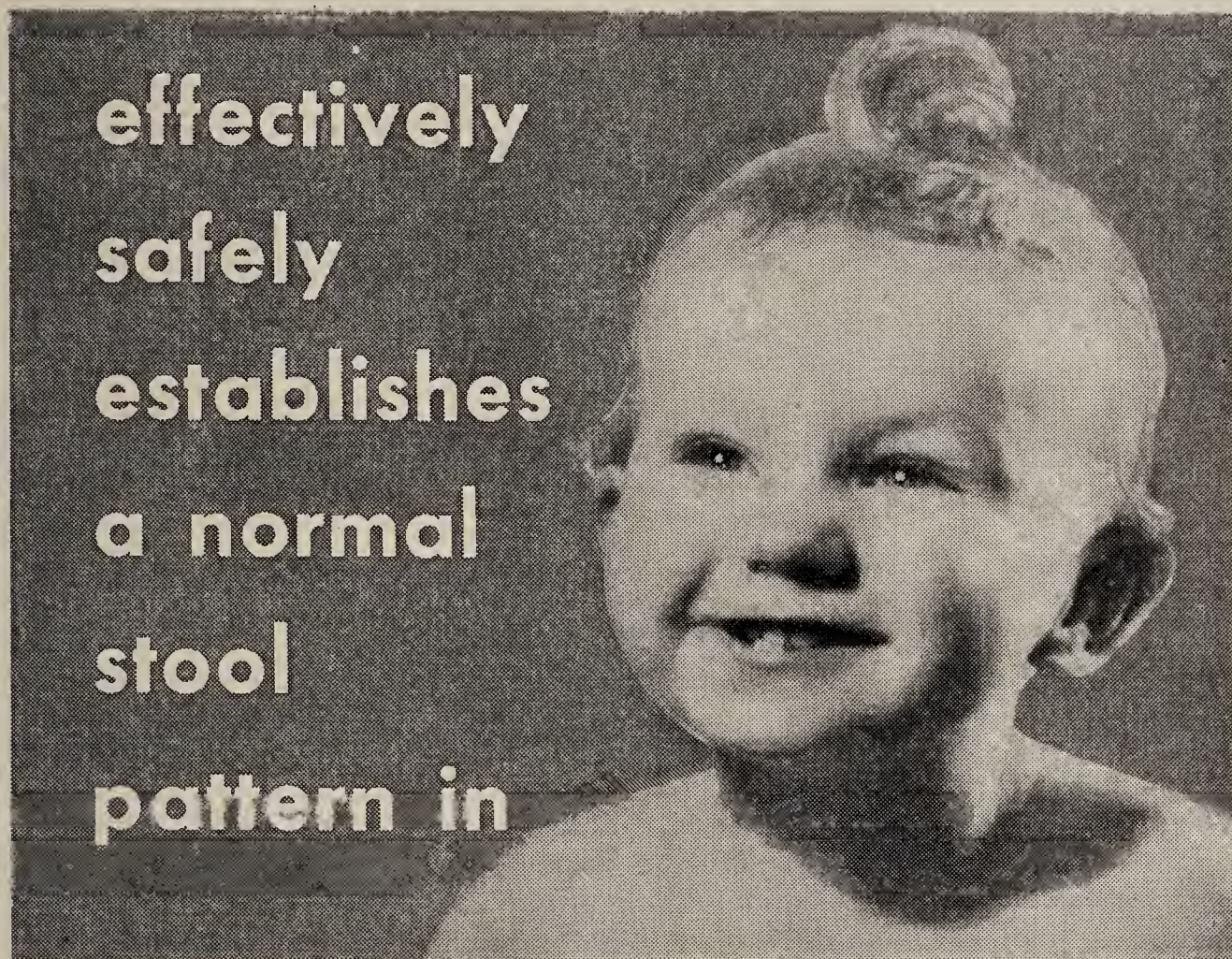
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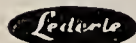
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EDITORIAL

THE PATHOGENESIS AND TREATMENT OF APATHY

The freshman enrolled in Medicine at this University is choice prey for the talons of extracurricular activities. His abilities may appall us, his enthusiasm frightens us, but his potentialities are many and great to our Medical Society. Pour water on this plant and short years later ask the chairman of Daffydil if he needs support or the Journal editor if he needs staff. Yet they cry that they are alone and that there is apathy! What happened to our seedling? How did apathy ever begin? Perhaps it is because some fellow plants turned out to be weeds or some master farmer sprayed him with vile chemicals hoping to make him grow better; or did we forget to water him?

The value of extracurricular activity in our university education as preparation for professional life is obvious and undoubtedly honest. No defence of it is needed here except to say that a doctor, more than most others, needs the training in social relationships afforded by this element. The medical student needs the Osler Society as much as he needs CAMSI examination reprints to enter the graduate body and hold his own in practice. The Medical Society organizations should be thriving in view of this essential fact but they are weak and dying with a lonely few left as watchmen. The stroma remains but the cells are disappearing. When we look at the prevailing codes and attitudes of the Faculty we have little wonder how this came to be. Three things happen to produce and maintain the apathetic medical student.

The first stab in the defeat of our spirited youth is *our* psychopathic neglect, something secondary to *our* ingrained apathy. We will eagerly sell him our textbooks, lab coats, microscopes and school ties, but we will not invite him into our *sancti* where he can be shackled with organizational scutwork. To this keen face, yearning for togetherness at any price, we mumble about how rough the course is and walk away pocketing the cash recovered from our ignorant purchases of the previous year. The first Arab fleeced him and turned him into the desert of six years of lectures, labs and more Arabs like the first, possibly never to come by the oasis of Acceptance. As will be shown later, he probably will not care.

The second thrust is made in the school when Running Brave meets the Chiefs. It continues to rot the piers of enthusiasm and participation until the student wears the mortarboard which symbolizes the flattening of his whole personality structure. The Chiefs engage in all manner of sport with the youngsters. Some make the courses incomprehensible rather than interesting; others make ominous threats like "There will be fatalities this year!" which cause an autonomic response in even the most well fixed rabbit; some must get a sadistic bang out of holding tests during the week of Daffydil; a few encourage open brawling among the confused and frightened neophytes by talking so low that they cannot be heard past the limited capacity of the front row. All spend hours at simple arithmetic calculating the class standings which, conspicuously posted, embarrass the low ranking, make the high too proud to be bearable and make the rest compete, rationalize and blandly lie to resolve the anxiety of being pitted against the greater odds of inheritance and a futile academic environment. The list of professional atrocities is lengthy and only a short indictment can be made here. The main charge concerns the inversion of the fact that the medical school and its staff exist for the medical student and should be operated to the latter's satisfaction in some, if not all, of its parts. He should command respect from the staff

where it is fitting and return it where such is earned. However, held by fear of being plucked, subject to a dependant future in postgraduate study or being a member of a misfortunate religion, he becomes subservient and aches to remain anonymous. A teacher can be anything he pleases with us—an ogre, a bore, a tyrant, a good man.

The third strike at our active, participating student is disintegrating because it comes from within. Bitterness and dejection cloud the bright star who would have been the ace Meds football player or the Music Club devotee. He watches his fellows slither into the library for lunch and decides that even eating may destroy his chances of success. His worries and apprehensions are petty to his seniors who blithely assure him with the words "Wait until next year if you think you've got it tough." Feelings of insecurity promoted by all about him, hammered by unreasonable demands for labour result in guilt and fear at the mere thought of spending time with Arts and Letters. The "reality" of foregoing the practices which make one different from a machine until he is done with medical school is "self-evident". He lives by the Auschwitz motto, *Arbeit macht frei*.

The apathy is cast; the mold is shortly hardened so that it may be impervious to any cajoling, coercion or recruiting carried on by the few hard-headed left staggering about the Medical Society Office and governing the politics and policies that the apathetic pay for as last token. The anemic, illiterate and defeated one is quite capable of openly spurning the undaunted ones as suckers and fools but more often he just hisses. To the clinician, the sick one is not so rocky; usually, he is but a stuttering, classifying and obsequious flap. Having never been easily accepted, owning little self-respect and lacking self-expression, it follows that he can generate little for extra-curricular activities. The shop is foremost and for all else there is apathy.

You will agree that the lesion, apathy, exists and that it is malignant. You may well ask if there is therapy. The answer is in the affirmative and the treatment is based on bolstering the general state of the individual before attempting to tease him out of the shell. The desired therapeutic ends are to put the student back into his rightful role as number one man and regenerating his self-respect as well as commanding a little humility and recognition from his present tormentors. Measures to be taken are abundant and only three examples are given:

1. It is time-honoured and fitting that a poor lecturer be booed and heckled until he either improves his presentation or flees.
2. Boycotting 8 o'clock lectures, useless laboratory periods and 90% of the Physiology term tests is an acceptable and decent way of indicating their annoyance to us.
3. Refusing to answer when the roll is called is only polite denial.

The number of items such as using the Banting elevators or not using student entrances is enormous and further evidence of our ignominious position.

The primary objective having been reached, the secondary benefits can be harvested by the Society people as well as the Faculty and countless of the sick public. Is it worth it? As mentioned before, the student doctor needs as much training and experience as he can get in both the cultural and scientific practice of medicine. Improving one's artfulness, physique and charm can only lead to a better and more efficient approach to his academic career so that the value of participation is doubled. Until some chap at one or other Institute nails together a protein, people will still be people, irrational, emotional, and whatever else nobody has yet classified. By continuing to exist in the bleakness that has been

described it is likely that we will become so molecule-mad we shall lose our patients to the crudeness of the chiropractors.

Daffydil, the Journal, Arts and Letters and the M.A.A. could be realized under a body named, say, the Medical Undergraduate Executive Council, were it not for that body's originators having a much different concept from that of law-giving government. They called it *The Medical Society* which indicates they envisioned a social organization in which every undergraduate could learn the *mores* and joys of medical people. The loss imposed by apathy is, therefore, ours alone.

L. E. S.

EDITOR'S NOTE:

Addition to article on WILSON'S DISEASE.

Vol. 37, 3, p. 79.

Current Views On Pathogenesis.

To follow immediately the words, . . . Krebs cycle activity. The other theory suggests there is a defect in the intracellular protein metabolism which leads to the formation of proteins with a high avidity for copper and hence the trapping of copper in these tissues.

THE MEDICAL SCHOOL AND THE UNIVERSITY

JOHN D. HAMILTON, M.D.*

THE opportunity to address a national conference of medical students and internes on the subject of "Medical Education" is one that comes but seldom, and the temptation to cover the subject is as difficult to suppress as the compulsion to omit nothing in an undergraduate lecture. One thing a teacher must learn, however, is to delete about one-half of the material he wishes to include. The problem is what to leave out. For example, the student finds it hard to believe that much of what is taught will ever be useful, so there is the desire to explain and apologize for the undergraduate curriculum. At the same time recognizing that you are about to leave the Medical School there is the wish to advise you of the necessity of continuing your medical education for the rest of your life, if you are sincerely interested in your profession. And, again, there is the plea not to set yourselves up as highly competent critics of every aspect of medical education, as so many of your colleagues have done and will continue to do. It is probable that no words of mine would have any influence whatsoever on what you now think of your teachers and what they teach, what you intend to do, and what you believe about the postgraduate education of the doctor. So I have decided to talk to you about the Medical School and the University.

Sir Winston Churchill, in an address to the Royal College of Surgeons, said that "The longer you can look back, the further you can look forward". This advice of a master historian is as applicable to medicine as it is to society in general

and thus I propose to outline briefly certain aspects of the history of Medicine.

The beginnings of medicine in pre-historic times can be quite accurately put together from the practices and myths of primitive peoples as they are recounted by Sir James Fraser in "The Golden Bough", and Robert Graves in "The White Goddess". The earliest society was matriarchal, and the earliest medicine was magic, either sympathetic or propitiatory. The one who practised the best magic became head of the tribe, and this superiority was gained by the more intelligent and observant individuals who learned the value of herbs as therapeutic agents. The head of the tribe, however, embodied many functions: physician, high priestess, often goddess and queen. Later the practice of the healing arts became delegated to a select group, the priestesses. When the matriarchal system was overthrown the upheaval of the community had far-reaching effects, even to the present day. Just when this reversal of the roles of male and female took place in terms of western civilization, we don't know, but it was probably when the Achaeans stumbled down from the north-eastern reaches of the Caspian Sea to Greece, dragging after them their god Apollo, the practice of monogamy, and other *mores* considered barbaric by the Pelasgians. The invaders did, over a period of time, modify their religion and make compromises with the natives to such an extent that the god was married to the goddess, and ultimately the Olympian family was created with Zeus as Sovereign of the Universe. You will note, however, that although Zeus was supreme, he was married to Hera, formerly the goddess of the natives. The children of the royal union were equally divided between male and female. This did not, however, completely appease the natives and worship of the many-named moon

*Department of Pathology, University of Toronto. This address was delivered at the National Conference of the Canadian Association of Medical Students and Internes, November 1959, as the first annual CAMSI Lecture on Medical Education.

goddess—Hera, Athena, Circe, Hecate, Persephone—survived in practices that in subsequent eras were called witchcraft. Over the centuries worship of the moon goddess persisted but became in the eyes of the Christian Church worship of the devil, and the Church throughout its long history in the dark ages and in mediaeval times, passed laws and prescribed punishment for the practice of witchcraft and invoking the devil. One thinks of sorcery as a figment of the imagination, and something that happened in the dark ages, but many of you will remember that 55 people were tortured and 20 executed in Salem, Massachusetts in the latter part of the 17th century, because they were accused of practising witchcraft. More recently in Mexico, in 1877, 5 alleged witches were lynched. In our modern society, however, the last remnant of witchcraft survives in the after-dinner liqueur, originally an infusion of herbs made from a secret formula, handed down by the women of the village from mother to daughter and used for medicinal purposes. Even this is now owned by men and has been so debased by the addition of sugar and alcohol that it doesn't even merit the distinction of being called a witch's brew.

In the further development of the patriarchal society the practice of medicine accompanied the practice of religion, both as the function of the priesthood. This alliance explains the myth of Aesculapius, a demi-god described as the father of the healing art. He is reputed to have been the son of Apollo and was rescued as an infant from a bonfire in which his mother and her paramour, Ischys, perished. After a life devoted to the healing art, he raised Glaucus from the dead and was burned to cinders by Zeus in a fit of jealousy. Zeus considered this usurpation of his powers. In this myth, the purpose of the destruction of the mother in the act of adultery is to discredit all female influence in the derivation of the gift of healing. Furthermore, the divinity of the father put the

seal of male supremacy on the art and thus on all matters medical. For some thousands of years the practice of medicine has been a profession for males, but today the male is no longer in the ascendant in most aspects of society and the female star is rising. While the full implication of this reversion to an ancient state will only unfold with time, as far as medicine is concerned I think we need no longer fear that the domination of the female will bring with it a return of witchcraft.

The fact that Aesculapius was the son of Apollo and a demi-god places the origin of the healing art in the temple, and this I think is important to appreciate as it confirms what I said before about medicine developing as magic; but as society became more civilized, religion and medicine became separate practices and both the function of the priesthood. It is important to realize that the expansion of knowledge of the healing art did not develop alone nor in isolation, but as part of the gradual acquisition of knowledge by men, using knowledge in the broadest sense to include the natural sciences, art and language. Religion, one of the dominant forces of early man, became more refined and separate from the arts and sciences although both were practiced and fostered by the priesthood.

Because of the alliance of art and science to religion, and their centralization in the temple, the degradation and downfall of paganism took medicine with it, so that the healing art fell into the dark ages with literature, science and almost all intellectual activity. In the East, however, medicine continued to flourish and to advance under the Iranian and Arab civilizations. Again it was allied to religion and the priesthood.

About the time that the Islamic civilization was waning Europe began to arise from its lethargy. The emergence of medicine as a distinct art and science occurred in the 11th century at Salerno with the founding of a school of medicine

by one Robert Guiscard. This really was the beginning of modern medicine, because, as I have tried to emphasize, until this time or rather until the fall of the Islamic empire, the arts and sciences of civilized men were intimately associated with the practice of religion and their development was fostered by those individuals whose principal function was religious. This included not only the priesthood but also, and to a less extent, the head of the state or tribe and the court which surrounded him.

We do not know much about the school at Salerno, which had been a notable port and centre of the old pagan civilization with a large temple and theatre and public buildings. This first school of medicine was not apparently part of a university, this came later, but its importance lay in the fact that medicine was recognized as a separate discipline. It was nearly a century later that the discovery at Amalfi of the pandects, a voluminous summation of Roman law, stimulated a general revival of intellectual curiosity.

In the 12th century, universities with faculties of law, theology and medicine were established, first in Bologna, then in Montpellier, Paris and Oxford.

At some time during the late 17th and 18th centuries the training of physicians outside the universities and the faculties of medicine became organized into independent schools. In Great Britain one of the most eminent was the Royal College of Physicians. Others developed in association with the voluntary hospitals. This was not a period of much progress in medical science and in the earlier part of the 19th century in Britain, the private or proprietary medical schools became incorporated into the universities or disappeared. Remnants of them persist in the three qualifications to practice that may be obtained in Great Britain today: the Licentiate of the Society of Apothecaries, Licentiate of the Royal College of Physicians and Member of the Royal College of Surgeons (called the Con-

joint Board Examination) and the university's degree, usually Bachelor of Medicine. In the United States, proprietary schools persisted throughout the 19th century and medicine fell to incredible depths of disrepute and charlatanism. Hundreds of schools arose, wherever a few practitioners banded together to accept students and charge fees. The students were sometimes kept only as long as they continued to pay fees, then were discharged with a diploma. Their training was preceptorship of the poorest type; the student simply observed his teacher practising. Public opinion finally brought the era to a close, following a survey and report of medical schools in the United States and Canada by Abraham Flexner, in which the importance of the university in providing a training in basic science is emphasized.

Throughout most of the Western world today, the medical schools and faculties are under the aegis of the universities. In Russia it is true that many medical schools exist as independent and separate entities. Guarantee of uniformity of standards is provided by the control of the Ministry of Health, which determines curricula and sets examinations. A similar control is in existence in many Western European countries, where the Ministry of Education fills a supervisory and standardization function, although the medical schools here are all affiliated with universities.

Now is the time, in my opinion, to reaffirm the relationship of the education of the physician to the university, because this is imperilled by influences that must be reckoned with, if the medical faculty is to maintain its standards. The past history of medicine, as I have tried to point out, is that it has flourished in close association with arts and science in general, that its segregation during the dark ages and again in more recent times resulted not only in stagnation but in regression. Most of the influences that beset medicine today have their origins outside the faculty or school, and come

under three main headings: postgraduate training of specialists; organized medicine; and standardization of the undergraduate program.

Of those external pressures one of the greatest is provided by the professional organizations that set up standards of professional competence. In the United States these are the specialty boards, and here, the Royal College of Physicians and Surgeons of Canada. With motives of the highest order these bodies throw an increasing burden on the staff and limitations on the graduate activities within the faculty. Their regulations demand postgraduate training in the laboratories and departments of the medical school. In addition they impose a burden on the academic staff in using them as examiners. An indirect influence is felt in the graduate courses offered by the University because they are given with an eye to the examination that must be passed by the candidate if he is to acquire specialist status. The graduate course is thereby in danger of being reduced to a cram session. What has happened to clinical departments is that their activities in the graduate sphere are often influenced by the preparation of graduate students for the examinations of the specialist organization. The value of this in terms of the advancement of scientific knowledge may be disputed.

Another external pressure is exerted by the medical associations, national, provincial and local, through demands for graduate courses and lectures; through criticisms of the medical curriculum and of the policies operating in teaching hospitals. The medical associations indicate the value they place on the teaching staff by absorbing so much of their time in providing courses, and, in fact, the major part of the scientific programs for their annual meetings, but they do not appear to recognize that the teaching staff can only be divided into a limited number of parts. The criticism of medical schools that is offered by the associations stems largely from individuals and is

often emotional, with its origins in undergraduate frustrations and dissatisfactions. Rarely such criticism is well considered and constructive. At other times the criticism arises from a difference of concept of the function of the medical school. In fairness one must admit that some of the criticism of medical education is justified and has its roots in the failure of the medical school to make its responsibilities clear to the medical profession.

The last of the external pressures that I shall mention is provided by the accreditation body, an arm of organized medicine that attempts to safeguard the standards but, at the same time, tends to impose a uniform pattern of medical education throughout North America. Although uniformity at a high level is commendable from the standpoint of professional competence, the restriction it imposes is contrary to everything a university stands for.

Within the faculty or school of medicine the greatest problem today is that posed by the changing social pattern and lies in the hospital. The teaching hospital in Canada has an enviable and hard-earned reputation built on integrity and contributions to the advancement of medical science. The heart of the teaching hospital has two parts, the physician appointed by the university and the public ward patient. This latter individual receives professional care without charge and in return contributes his signs, symptoms, progress and reaction to therapy to the record of disease. Both of these individuals, the doctor and the patient, are integral parts of undergraduate teaching, of research and of postgraduate training. The university therefore has a vested interest in each, and it is incumbent upon it to protect both doctor and patient. The introduction of hospitalization in most of Canada has reduced the cost of sickness to the individual, so much so that the patient who formerly had difficulty in meeting expenses in a public ward bed now can

afford semi-private accommodation. He can obtain this for as little as \$5.00 per day. Within a year of the introduction of hospital insurance in Ontario, one finds that the demand for private beds has increased markedly while the wards are in danger of being depleted of patients available for teaching. Today many of the public beds are being occupied by individuals who would prefer a private bed but cannot get it. When the private patient moves into a public ward he passes out of the control of his personal physician and no longer pays professional fees. Thus the physician or surgeon on the staff of the teaching hospital forfeits professional fees on patients who must accept ward accommodation because there is no other available. This causes loss of income to the physician on the teaching staff, an individual who is already devoting much of his time to undergraduate teaching with only a token honorarium. When one adds these facts to the greater proportion of public versus private beds in teaching hospitals, it is easy to see that the desirability of teaching posts is rapidly declining.

Another problem within the school is the necessity to undertake productive research. By productive I mean the publishing of papers in order to keep the name of the medical school and the university in the fore. There is great competition in North America in the field of medical research; for funds, for personnel, and for prestige. While it has been recognized for many years that the best teachers are those who engage in some form of investigation, the pendulum has swung too far, and now one of the principal means of judging a department in the faculty is according to the number of publications. Similarly, teachers may obtain appointments on their research ability alone. This overemphasis on the scope of the investigations and the magnitude of their cost already afflicts some departments in our medical schools in Canada.

You may well ask me at this point

what is the responsibility of the medical faculty of the university? It is quite simply to teach the art and science of medicine and to foster research. As we have seen from a glance at the past, this can only be done in the atmosphere of the university, where there is a tradition of high standards and where the faculty of arts can teach us how to communicate and provide us with stimulation and knowledge through contacts with pure science. What is required is a definition of the limits of responsibility for the faculty of medicine. First and foremost it is the teaching of undergraduates and secondly, the conduct of research to broaden knowledge. Outside of these functions fall postgraduate training for professional competence and the continued education of the practising physician in order to maintain good standards of medical care. These both really come under the heading of graduate training and constitute the greatest burden on the medical schools today. One may argue that they are not rightly a responsibility of the university, but if the university is to provide leadership, then it should indicate how the demands for such training may be met. The question is not simple but complex, because hospitals require internes to assist with the provision of medical care to the patient while the internes require the supervision and the time of the medical staff. In other words the university through its staff is contributing to training while the hospital is also contributing in creating a sufficient number of posts and in providing an honorarium. The problem of medical care within the hospital could be met at less expense by hiring a few doctors at a reasonable salary. To date we have not solved the problem of responsibility for graduate training.

Perhaps I have not made clear up to this point that there is a faint movement, so far unspoken but one senses its power, to leave the education of the physician in basic science to the university, but to remove the student from the control

of the university when he reaches the clinical years, when he should be given a practical training by practical men. Should such a separation develop, then, in my opinion, medicine will suffer as it did during the 18th and 19th centuries. The danger to the undergraduate is that he will be exposed to training in techniques and not continue to be educated in principles and method. In the hospitals there is so much emphasis on post-graduate training that the undergraduate and his education may be overshadowed. But remember that unless the undergraduate has been imbued with a solid grounding in the principles of medicine he will never make a competent practitioner nor a good specialist.

It is not my intention to discuss the undergraduate curriculum but I will say that its objective, to repeat what has already been said, is to provide the individual with the framework of medical science in the form of principles and method. The doctor must continue for

the rest of his life to build his knowledge of disease. What is intended in the undergraduate course is to equip the student with the means to deal with unknown situations and diseases and not to give him a comprehensive account of every disease he may encounter because such an attempt would fail from its very size.

En fin de compte, je voudrais vous prier de tenir le concept de la Faculté de Médecine comme un part intégral de l'Université. Aujourd'hui le matérialisme, une force puissante dans la vie nord-Américaine, menace la forteresse de notre culture, l'Université. Dans notre profession, il se manifeste particulièrement dans la poussée vers la spécialisation et la concurrence de la formation post-scolaire. Il faut garder la Faculté dans la tradition de l'Université si nous voulons la protéger contre les influences matérialistes de la vie moderne, et si nous voulons la maintenir dans la poursuite de l'idéal.

CARCINOMA OF THE PROSTATE

This is the commonest malignancy occurring in the male. The early forms are potentially curable provided that they are diagnosed at this stage. For this reason the author recommends that a rectal examination should be part of every physical examination in males over the age of 40. If a suspicious lesion is found biopsy is obligatory. If clinical and laboratory studies indicate that the tumor has not extended beyond the pseudo-capsule of the prostate the treatment of choice is total surgical removal of the prostate and seminal vesicles.

J. A. C. Colston, Jr., Med. Clin. of N.A. Nov. 1959.

BROAD SPECTRUM ANTI-HELMINTHIC

Dithiazanine (Telmid, Lilly) is a new oral drug proven effective in whipworm, ascaris, threadworm and pinworm infestations. Studies now seem to indicate that it may also be effective against beef and dwarf tapeworm. Its toxicity is virtually nil. The usual dose is 100 mg. three times daily for five to ten days.

Good
+ practical

HORNER'S SYNDROME

R. A. HART, 6T1

IN 1869, Frederick Horner, a Swiss ophthalmologist practising in Zürich, described a syndrome which is unsurpassed as a practical lesson in applied anatomy and physiology.

ANATOMY

The centre of the sympathetic nervous system is in the lower part of the lateral wall of the third ventricle. Fibres arising in this part of the hypothalamus descend through the brainstem in the dorsal part of the reticular formation and enter the spinal cord. Fibres from the spinal cord arise from the lateral column of the gray matter and emerge in the anterior nerve roots of C₈ to T₄. The preganglionic fibres run uninterrupted to the superior cervical ganglion through the inferior and middle cervical ganglia. The synapse between the preganglionic and postganglionic fibres occurs here. The anterior branches of the superior cervical ganglion ramify on the common carotid artery as the internal carotid nerve, which ascends by the side of the internal carotid artery. It divides into two branches after entering the carotid canal in the temporal bone. The medial branch forms the medial part of the internal carotid plexus, which gives branches to the internal carotid artery and communicates with the oculomotor, trochlear, ophthalmic and abducent nerves, and with the ciliary ganglion. In addition to fibres which run with the internal carotid artery, another group follow the external carotid artery and its branches. By these routes, therefore, sympathetic nerves run to the following structures:

- (1) involuntary muscles of levator palpebrae superioris (Müller's tarsal muscle)
- (2) dilator pupillae muscle
- (3) sweat glands of the face
- (4) blood vessels of the eye.

SIGNS COMPRISING HORNER'S SYNDROME

- (1) ptosis
- (2) miosis
- (3) anhidrosis and increased temperature over the face
- (4) enophthalmos

The syndrome is almost always unilateral.

ETIOLOGY

Horner's syndrome is produced by an interruption of the sympathetic pathways described. A classification of causes can be made by anatomical levels.

Brain Stem

Lesions at this level are found particularly in the reticular formation in the lateral medulla. Sometimes they interrupt pathways descending to the cord from the sympathetic centres in the hypothalamus. The lesion is often due to a vascular accident, commonly a thrombosis of one of the posterior inferior cerebellar arteries. It may rarely be due to a pontine tumor, multiple sclerosis, encephalitis or acute anterior poliomyelitis.

Cervical or High Thoracic Cord

The lesion in this area involves descending sympathetic fibres in the anterolateral columns or their junctions with lateral horn neurons, as in syringomyelia, hematomyelia and cord tumors.

Cervical and Thoracic Anterior Spinal Roots, or White Rami

Lesions causing trouble at this level include pachymeningitis or radiculitis. There may be pressure from an aortic aneurysm or neoplasm high in the mediastinum or at the thoracic inlet. Trauma to these fibres may accompany penetrating wounds, surgical procedures in the neck, or injury at birth to structures in the lower neck area.

Cervical Sympathetic Trunk

This is the commonest site for interruption of sympathetic pathways to the head. Benign or malignant tumors and damage by surgical procedures comprise the main lesions.

Carotid Sympathetic Plexus

Lesions in this area are infrequent. An internal carotid aneurysm or thrombosis may be at fault or rare tumors of the adjacent Gasserian ganglion may be present. The resulting defect in sweating is commonly limited to the forehead.

It is of interest that in 25% of cases there is no demonstrable cause for a Horner's syndrome. A congenital form has been described.

PHYSIOLOGY

- (1) The ptosis is due to interruption of the sympathetic fibres supplying smooth muscle of the upper lid. The ptosis is partial and the lid can be raised voluntarily through the action of levator palpebrae superioris, innervated by an intact oculomotor nerve.

- (2) The miosis is due to paralysis of the dilator of the pupil. There is unopposed action of fibres of the sphincter pupillae supplied by the parasympathetic system.
- (3) The anhidrosis and increased temperature over the face are due to loss of sympathetic innervation to sweat glands and blood vessels, respectively.
- (4) Measurable enophthalmos is rare. The eye appears to be retracted, but this is an illusion caused by the slight droop of the lid. It is unlikely that the rudimentary fibres making up Müller's orbital muscle play any part in the syndrome.

ACKNOWLEDGMENT

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CHLORAMPHENICOL AND GAMMA GLOBULIN

The authors report on a clinical trial of the combined use of chloramphenicol and gamma globulin. Patients with infections which failed to respond to other antibiotics or to chloramphenicol alone showed remarkable response to this combination. Moreover, in other patients they found that this combination reduced the likelihood of resistance and speeded up recovery.

Antibiotics Annual, 1957, 1958.

ANTICOAGULANTS FOR OUTPATIENTS

The authors reviewed 59 cases in which some thrombotic episode indicated a therapeutic trial of anticoagulants. These patients were discharged from hospital and were taking daily doses of dicoumerol. The dose was regulated by bi-monthly one-stage prothrombin times. In a period covering approximately eleven months 18 bleeding episodes were encountered and the prothrombin time was over 30 seconds in most of these cases. This represents an incidence of 30 per cent.

Grant and MacMillan, C.M.A.J. marl. 1958.

HEREDITARY ANOMALIES OF HUMAN METABOLISM

R. G. LEE, 6TO

IN 1908 Sir Archibald Garrod opened up an entirely new field in both clinical medicine and basic sciences with his classical description of four clinical conditions which he termed "Inborn Errors of Metabolism". Garrod put forward this new concept in the famous Croonian Lectures delivered before the Royal College of Physicians. The four original inborn errors of metabolism which he described were alkaptonuria, albinism, cystinuria, and pentosuria. There were several criteria which led Garrod to believe that these conditions were inherited disorders. First, in most cases the onset of the abnormality could be dated to the first few days or weeks of life. In addition, a number of the inborn errors showed a familial occurrence and it was noted that these metabolic errors seemed to occur more frequently among the offspring of consanguineous marriages. It is now known that the latter factor is a condition which favours the appearance of recessive traits. Garrod also observed that his inborn errors were of a relatively benign and non-progressive nature and therefore compatible with an almost normal life expectancy.

Since 1908 the group of inherited metabolic abnormalities has grown from the original four conditions described by Garrod to a total of more than fifty diseases and each year additional, formerly idiopathic diseases are being found to fit into this group.

With the many new discoveries in the fields of biochemistry and genetics some of Garrod's original ideas have required modification. He believed that the inborn errors could all be explained on the basis of the absence or failure to function of a particular enzyme, and while this concept is true in many cases, it can no longer be applied to all the diseases within the group. While the original four inborn errors are aptly described as being

relatively benign and non-progressive in nature, there are many inherited diseases such as porphyria, phenylketonuria and congenital galactosemia which have profound effects on the health of the individual. A knowledge of these diseases became even more important when it was discovered that at least some of them responded to various forms of treatment, and a few could be completely remedied by dietary changes if a diagnosis was made early enough in life.

To describe even briefly all of the diseases now recognized as inborn errors of metabolism would be a prodigious task and would require nothing short of a complete volume. Therefore, this article will necessarily be a rather incomplete review of a very broad and rapidly widening field of study. What we propose to do is to consider inherited metabolic disorders of four main groups of compounds which help constitute the body chemistry: the proteins and amino acids, the carbohydrates, the lipids and the pigments. For each group one or two specific diseases will be described as examples of inherited disorders of that particular type of chemical compound. Then we shall proceed to consider some of the more recent knowledge which has developed in the field of biochemical genetics, and some of the general mechanisms by which these metabolic diseases can be inherited.

I DISTURBANCES OF PROTEIN AND AMINO ACID METABOLISM.

This is the area in which most of the original work was done on inborn errors of metabolism. Three of the original four diseases described by Garrod fit into this group. Many diseases resulting from abnormalities of the serum proteins are now recognized as inherited metabolic disorders. Congenital afibrinogenemia,

several types of hemophilia, and congenital agammaglobulinemia are all examples of inherited diseases of the serum proteins. Then we also must consider disturbances of amino acid metabolism such as alkaptonuria, phenylketonuria, tyrosinosis, albinism, and cystinosis. Several of these latter diseases are closely related disorders of phenylalanine-tyrosine metabolism.

Alkaptonuria

Loewy and Neuberg, two early workers in the field of metabolic errors, once said, "It is an old experience that nature often grants us through her errors unexpected insights into her secrets which are otherwise a closed domain." This statement is especially true of alkaptonuria. It is not an important clinical entity, occurring very rarely and having an incidence estimated to be somewhere between one in 250,000 and one in 10,000,000. However, studies of alkaptonuria have contributed immensely to our knowledge of intermediary metabolism. In 1908 Garrod said, "Of inborn errors of metabolism, alkaptonuria is that of which we know most and from the study of which most has been learnt."

The characteristic feature of this disease is the excretion of a urine which turns dark brown or black on exposure to air. The substance responsible for this colour change was originally termed "alkapton" and it is now known to be homogentisic acid, one of the normal intermediary metabolites formed in the body from tyrosine. The excretion of this substance commences at birth and persists throughout life, and it is now almost certain that the condition represents an inherited recessive trait. Homogentisic acid is a strong reducing substance and some of the cases reported in the literature were originally diagnosed as diabetes mellitus. However, the fact that it does not ferment and does not exhibit optical activity aids in differentiating homogentisic acid from glucose in the urine.

The other manifestation of alkaptonuria is a condition known as ochronosis, which usually does not appear until the second or third decades of life. Ochronosis is a descriptive term referring to the pathologic deposition of a black pigment (now believed to be a polymer of homogentisic acid) in various areas of the body such as cartilage, fibrous tissues, tendons and atheromatous plaques. This deposition eventually results in an arthritis of the large joints and although patients with alkaptonuria can live to a ripe old age, many of them become severely crippled with arthritis.

Alkaptonuria is an example of the accumulation of an intermediate metabolite normally present in only very small amounts. In individuals with this disease the enzyme which normally oxidizes homogentisic acid is missing from the liver, and the metabolite accumulates to the point where it is excreted in the urine and deposited in the tissues.

Phenylketonuria

This disease is particularly interesting and important because it results in severe mental deficiency. Moreover, the serious manifestations of the disease can be completely avoided by correct dietary management providing that the diagnosis is made early in life. Phenylketonuria results from a mutation in the gene which normally controls the enzyme, phenylalanine hydroxylase. It is transmitted by the autosomal recessive mechanism and therefore a person suffering from the disease must have both abnormal genes. In other words, both parents must be heterozygous for the mutant gene and this fact accounts for the relative infrequency of the disease (one in 25,000).

The absence of phenylalanine hydroxylase from the liver results in a failure of conversion of phenylalanine to tyrosine along the normal metabolic pathway. Phenylalanine accumulates in large amounts and is converted to several other metabolites, including phenylpyruvic acid which appears in the urine.

This is easily detected by the olive green colour produced by the addition of ferric chloride to the urine.

Evidence of mental retardation does not usually appear until several months after birth and the critical period for this disease is between six months and four years of age. During this period the brain is undergoing biochemical maturation involving complex myelination reactions and it is felt that the large amounts of phenylalanine accumulating in the body have harmful effects on these delicate processes. However, if the child is given a diet containing little or no phenylalanine, he will develop normally and show no evidence of mental deficiency. Therefore, this disease is an example of one of the inherited disorders of metabolism in which the clinical manifestations can be avoided although the basic enzymatic deficiency remains unchanged. The success achieved in treating phenylketonuria provides hope that other less well understood metabolic abnormalities may in the future also prove to be curable.

Other related conditions

Two other diseases, tyrosinosis and complete albinism, are also most likely inherited blocks in the metabolic pathways of phenylalanine and tyrosine. These are extremely rare conditions.

II DISTURBANCES IN CARBOHYDRATE METABOLISM

The intermediary metabolism of carbohydrates is now fairly well understood and when we consider the large number of reactions and enzymes involved, we can compile a long list of possible inherited metabolic disorders for this group. Some of the better known conditions which fall under this heading are pentosuria, fructosuria and galactosemia. In addition, there are several types of glycogen storage disease now recognized. Perhaps the best known of these is von Gierke's disease or hepatorenal glycogen

storage disease. Just recently, hereditary spherocytosis has been found to be an inherited disturbance in the glycolysis of red blood cells and, therefore, it also fits into this group.

Congenital galactosemia

Like many of these inborn errors of metabolism the term congenital has been attached to the name of this disease. Hereditary would be a much more appropriate adjective, but because of prolonged usage we shall retain the original term. Congenital galactosemia was first described by Von Reuss in 1908. Clinically, it is characterized by vomiting, lethargy, failure to gain weight and liver enlargement, commencing a few days after birth. Jaundice in the neonatal period is a common feature, and ascites and edema may also appear.

Galactosemia is transmitted by an autosomal recessive gene and the defect has been noted among siblings in about one-half of the cases reported. The metabolic defect is now known to involve the enzyme P-gal-uridyl-transferase, which normally catalyzes the conversion of galactose-1-phosphate to glucose-1-phosphate. The resulting biochemical abnormalities are numerous. There is an accumulation of galactose-1-phosphate in the erythrocytes. Galactose itself accumulates in the blood and tissues and spills over into the urine. Pathological changes occur in many organs as a result of the galactose accumulation. Liver cirrhosis may develop; renal damage is manifested by amino aciduria; and cataracts are found in the lens of the eye. Associated with the high blood galactose concentrations, there is a decreased level of blood glucose which may cause convulsions and mental deficiency.

The diagnosis of this condition should not pose too much difficulty for the alert physician. Along with the clinical features there is a non-glucose reducing substance present in the urine. Further tests reveal this substance to be galactose and also demonstrate excessively high

galactose levels in the blood. The galactose tolerance curve is characteristically elevated. One difficulty which is encountered is the fact that many of the newer tests for sugar in the urine are specific for glucose and the presence of galactose will not be suspected unless one of the older non-specific tests is used (Benedict's test).

Fortunately, this disease which can produce severe pathological changes and even a fatal outcome, is another condition which can be completely remedied by early recognition and dietary management. No long term effects will occur if all milk and milk products containing lactose and galactose are withdrawn from the diet in the first few weeks of life. Nutramigen or protein hydrolysates are introduced into the diet as milk substitutes. As the child gets older he is able to tolerate small amounts of milk in the diet, presumably because an accessory pathway of galactose metabolism develops in the liver.

III DISTURBANCES OF LIPID METABOLISM

The study of lipid metabolism is a very active field at the present time and a great deal of research is going on, aimed especially at learning more about the etiology of atherosclerosis. Many disorders of lipid metabolism have been shown to have a definite hereditary basis but, as yet, relatively little is known about the primary genetic and biochemical mechanisms. Included in this group are idiopathic hyperlipemia, primary hypercholesterolemia, Gaucher's disease, Niemann-Pick disease, amaurotic familial idiocy, and lipochondrodystrophy (Gargoylism).

Niemann-Pick disease

This is a rare, usually fatal disorder of lipid metabolism with widespread manifestations. The clinical picture was first described by Niemann in 1914 and a few years later Pick presented the pathological features of the disease. About 80 cases have been reported in the world literature.

The infant may appear normal at birth, but signs of physical and mental retardation soon appear. The clinical picture is one of gradually increasing debility and neurological deterioration with wasting of the extremities and marked protuberance of the abdomen due to hepatosplenomegaly. A cherry red spot is present in the macula lutea in somewhat less than half the patients. Marked anemia is a characteristic feature and the peripheral blood smear sometimes shows vacuolization of the agranulocytes. The infant becomes apathetic and dull and is described by Hsia as, "an anemic and emaciated idiot with a large abdomen." Death usually occurs before the age of five years.

The pathological findings in this disease consist of a generalized distribution of large pale cells with a foamy-appearing, vacuolated cytoplasm in all organs of the body, but especially in the liver, spleen, lung, lymph nodes and bone marrow. There is marked involvement of the central nervous system manifested by degeneration and swelling of the ganglion cells.

The disease is believed to be transmitted by an autosomal recessive gene, but the exact chemical nature of the metabolic abnormality is not yet known. In normal lipid metabolism the reaction by which ceramide is converted to sphingomyelin is a reversible one, and it has been suggested that in Niemann-Pick disease the mechanism for reversing this step is defective. This would result in an accumulation of sphingomyelin in the various tissues, accounting for the hepatosplenomegaly, mental deterioration and changes in the ganglion cells.

Diagnosis of the disease is confirmed by finding the characteristic foam cells in biopsies from bone marrow, spleen, liver or lymph nodes. As yet, no effective treatment has been found for this fatal condition.

IV DISTURBANCES OF PIGMENT METABOLISM

Fitting into this classification are a

number of very interesting diseases including three types of methemoglobinemia, hepatic porphyria of which there are also three distinct forms, and familial non-hemolytic jaundice. For the purposes of illustration we shall consider the extremely interesting and dramatic illness, acute intermittent porphyria.

Acute intermittent porphyria

As the name signifies, this disease is characterized by intermittent attacks presenting with a wide variety of abdominal and neurological manifestations, punctuated by periods of remission when the patient is completely free of symptoms. It appears that the disease is transmitted by an autosomal dominant gene. Waldenstrom has studied the genetics of the disease in Sweden and has found an incidence of 1.4 per 100,000. However, in Lapland the incidence increases to figures as high as 1 in 100.

One of the commonest manifestations of the disease is periodic attacks of severe abdominal pain. The clinical picture often leads to a mistaken diagnosis of an acute abdominal condition, and many of these patients have a picturesque display of surgical scars on their abdomens having been operated on in error. The other common abdominal complaint is severe, obstinate constipation.

The neurological manifestations are numerous, but usually commence with peripheral neuropathy characterized by pain in the limbs, weakness, and sometimes marked flaccid paralysis. In more severe cases there is bulbar involvement with difficulty in swallowing and respiration. There may be a weak, high-pitched voice resulting from vocal cord paresis.

Psychic changes are another common feature. A pseudohysteria is frequently observed and some cases may progress to a frank psychosis which is often wrongly diagnosed as schizophrenia. The autonomic nervous system is also involved in acute porphyria.

The characteristic biochemical finding in this disease is the presence of abnor-

mally large quantities of porphobilinogen in the blood and urine. The porphobilinogen excreted in the urine changes to uroporphyrin on standing, imparting the characteristic port-wine colour to the urine.

An extensive search has been made for the metabolic error which results in acute porphyria, but at present the pathogenesis of the disease is still not entirely clear. The normal metabolism of the porphyrins is rather complex, but in brief the main features are as follows. Two molecules of d-aminolevulinic acid condense to form the monopyrrole porphobilinogen. This compound is then acted on by two enzymes which convert it to uroporphyrinogen I and uroporphyrinogen III, which are in turn converted to other products. It seems logical that there is a block somewhere along this metabolic pathway resulting in the accumulation of porphobilinogen and possibly also d-aminolevulinic acid, but its exact location remains to be discovered. Also, it has not yet been possible to explain the abdominal and neurological symptoms on the basis of these chemical findings.

Treatment of acute porphyria is supportive and symptomatic, no definitive cure having yet been discovered. These patients should avoid alcohol, barbiturates and hepatotoxins which for some reason tend to precipitate attacks.

MECHANISMS OF INHERITANCE AND BIO-CHEMICAL ASPECTS OF GENETICS

Until recently the actual chemical mechanisms of heredity and the precise actions of genes have been a rather vague topic, but in the past decade rapid advances in the field of biochemistry have contributed immensely to our knowledge of genetics. There has in effect been a union of the two sciences resulting in an entirely new and enticing field of study, biochemical genetics.

For some time it has been known that hereditary characteristics are transmitted by the duplication of chromosomal material during cell division. It has also

been common knowledge that nucleic acid is present in the chromosomes. But only recently has sufficient evidence accumulated to prove beyond doubt that the DNA nucleoprotein, the basic constituent of the genes, is the actual hereditary substance.

In the light of this knowledge it might be worthwhile to consider briefly the chemical nature of nucleoproteins. Nucleoproteins consist of nucleic acids (either DNA or RNA) linked to a specific protein. The nucleic acids are actually chains of nucleotides, substances consisting of a nitrogen-containing base linked to a five-carbon sugar molecule, which is in turn linked to inorganic phosphate. The nitrogen-containing bases in DNA are the purines, adenine and guanine, and the pyrimidines, cytosine and thymine. RNA differs in that uracil is present in place of thymine. The DNA molecule is a helical structure consisting of two parallel nucleotide chains twisted about a central core. There are approximately 25,000 nucleotide units in a DNA molecule, resulting in a molecular weight in the vicinity of 8,000,000. The important point to make here is that the four bases, adenine, guanine, cytosine, and thymine could be arranged in any order along the nucleotide chain and simple mathematical permutations reveal that it would be theoretically possible to have an almost infinite number of distinctly different nucleic acids. Actually it has been estimated that there are between 5,000 and 25,000 genes in a human cell, each gene consisting of a nucleoprotein molecule or a section along the helical chain.

Two basic concepts must be kept in mind at this point. First, genes (i.e. nucleoprotein) are able to reproduce themselves. It has been suggested that in the process of cell division a molecule of nucleoprotein represents a mold or template on which an exact image of itself can be manufactured from materials already present in the cell. In this way identical characteristics are transmitted from parent to daughter cells. Secondly,

it is now believed that genes act as catalysts in the synthesis of proteins and in particular, the synthesis of specific enzymes. Knox compares a nucleotide chain to a tape on which the sequence of purines and pyrimidines represents coded information. This coded information directs the order in which the amino acids will be arranged in the protein molecule. The question may arise here as to how DNA, which is located almost exclusively within the nucleus of the cell, can control protein synthesis which we know takes place in the cytoplasm. This stumbling block is overcome with the hypothesis that DNA transmits its coded information to RNA which then passes out of the nucleus into the cytoplasm. In the cytoplasm RNA is found as a constituent of microsomes and endoplasmic reticulum, substances which are known to be involved in protein metabolism. Therefore RNA can be likened to a working copy of the master plan contained in the DNA.

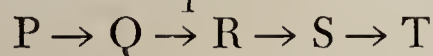
After this brief venture into the field of nucleoprotein chemistry it becomes more clear how a change or mutation in a gene can result in a corresponding alteration in the protein molecule of an enzyme. If the sequence of purines and pyrimidines in the DNA is juggled, there will be a resulting alteration of the amino acids in the protein molecule. The enzyme may be completely absent or changed in such a way that it can no longer carry out its normal function, and pathological changes appear in the organism. The theory that each gene controls the specificity of a single enzyme is a very attractive one and helps explain many of the hereditary metabolic abnormalities.

One of the best examples supporting this hypothesis is the well known abnormality of the red blood cells, sickle cell anemia. In a recent, remarkable study of the hemoglobin molecule, Ingram demonstrated that the clinical features of this disease result from an alteration in a single amino acid particle among the

three hundred amino acids which make up the hemoglobin molecule. In sickle cell hemoglobin a glutamic acid particle present in normal hemoglobin is replaced by valine. This very small chemical abnormality results in profound physiological changes. In the deoxygenated form the altered hemoglobin is very insoluble. It crystallizes inside the cells, distorting the cells to the characteristic elongated sickle shape. These abnormal cells tend to clog in the small vessels and hemolyze, producing the thromboses and anemia characteristic of the disease.

Metabolic blocks

We have seen how alterations in the nucleoprotein structure of genes can produce abnormalities in the specific enzymes controlled by these genes. Now, let us proceed to consider the possible metabolic errors which could arise from the lack, partial lack or inhibition of a single enzyme. Snyder has outlined this very clearly by using as an illustration the theoretical sequence of reactions:



Each arrow represents an enzyme capable of converting one substance to another. Let us consider the situation in which the gene catalysing the conversion of R to S has undergone mutation so that it is no longer effective in carrying out its function. The resulting metabolic abnormality may be manifested in several different ways.

The substance R may accumulate and be stored in the body resulting in pathological manifestations. This is probably what happens in Niemann-Pick disease in which there is a genetic failure to degrade sphingomyelin resulting in the accumulation of this lipid in reticular and other cells.

Another possibility is that the substance R, rather than accumulating in the body, may be excreted in the urine resulting in symptoms such as stone formation, hematuria and urinary frequency. An example of this type of mechanism is the disease xanthinuria in

which there is an abnormality or absence of the enzyme xanthine oxidase, resulting in a failure to convert xanthine to uric acid.

If the reactions taking place before the block are reversible, there may be an accumulation of substance P rather than substance R. This situation occurs in one type of glycogen storage disease of the liver.

It is easily seen that a metabolic block in the conversion of R to S will result in a deficiency or complete absence of substances S and T. In albinism there is a genetic dysfunction of the enzyme tyrosinase so that tyrosine is not oxidized along the pathway leading to melanin.

There are still other possibilities which will just be mentioned briefly here. A block at one point in a metabolic pathway may result in the diversion of metabolism along alternate pathways leading to the production of large amounts of substances normally absent from the body or present in only small minute amounts. These substances may produce profound pathological effects, as in phenylketonuria. The mutant gene may result not merely in a lack of the specific enzyme, but in the presence of a demonstrably functional but somewhat different enzyme. This enzyme could act in such a way as to convert R to A, an entirely new substance which could conceivably produce pathological changes in the body. Sometimes the accumulation of substance R may manifest itself by the inhibition of another unrelated enzyme system.

Therefore, it is seen that when a single enzyme fails to function, the theoretical possibilities of metabolic abnormalities are quite numerous and the pathological effects on the body may be quite profound.

CONCLUSIONS

In this brief essay we have not been able to mention more than a few of the better known inborn errors of metabolism. As mentioned previously there are

at present over fifty diseases which are known to belong to the group of inherited metabolic disorders. Moreover, with the knowledge that a human cell contains several thousand genes, each of which could conceivably undergo mutation, we can imagine that there are many other, as yet unrecognized, inborn errors of metabolism. We hear a great deal today about the dangers of the increasing level of radiation in the world and the effect it may have in producing mutation of genes, so it is not entirely unreasonable to suppose that the incidence of inherited metabolic diseases may show an increase in the future.

Some of the common diseases for which an inherited metabolic basis has been suggested are diabetes, rheumatoid arthritis, coronary heart disease and schizophrenia. The etiology of schizophrenia, in particular, is entirely unknown at present and the finding of a familial incidence in some cases and biochemical abnormalities in many affected individuals provides hope that this disabling mental disorder may be found to be the result of an inherited enzyme abnormality which could possibly be corrected or modified.

Knox and others have suggested that congenital structural abnormalities such as cleft palate and congenital heart disorders may be the result of an inherited biochemical abnormality occurring at a critical period in the development of the fetus. The study of biochemical reactions taking place during the prenatal period is obviously very difficult and much work remains to be done in this field.

It is known that certain individuals have severe reactions to drugs and chemicals which are harmless for the majority of the population. Motulsky has pointed out that certain drug idiosyncrasies may be due to genetically determined factors. As examples, he mentions the hemolytic anemia which some people develop in response to average doses of primaquine and the prolonged apneic reaction seen in some individuals after they are given succinylcholine.

Finally, any discussion of inborn errors of metabolism brings up the question of the relationship between heredity and environment. Garrod originally believed that these inborn errors manifested themselves very shortly after birth, but we now know that many inherited diseases such as Huntington's chorea, do not make appearance until the third or fourth decades of life. Therefore, we cannot help but wonder just how great a part environmental factors play in bringing about the onset of these diseases. Perhaps some of these inherited disorders could be prevented or modified by control of the environment.

SUMMARY

Inborn errors in the metabolism of amino acids, carbohydrates, lipids and pigments have been discussed with examples from each group. The biochemistry of nucleoproteins and the basic mechanisms of inheritance have been described, with emphasis on the theory that a gene controls the specificity of a single enzyme. The theoretical possibilities resulting from a metabolic block were considered and, finally, a brief look was taken into the future of biochemical genetics.

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NEWS AND NOTES

The following scholarships were announced following the Senate meeting on December 11, 1959: The Frosst Scholarship was won by J. Schatzker; The B'Nai B'Rith Scholarship was won by M. J. Abrams; The Baptie Scholarship was won by M. L. Lipson; Medical Alumni Scholarships were won by F. W. Furlong, R. Baumal, F. Rosen, M. L. Jerry, J. Schatzker.

Dr. Clement McCulloch was guest speaker at the Montreal Ophthalmological Society's meeting at the Royal Victoria Hospital. His subject was "The Mechanical Complications of Surgical Penetrations of the Eye".

Dr. Frank B. Walsh of Johns Hopkins University delivered the second Walter W. Wright Lecture on Ophthalmology at the Academy of Medicine, on "Trauma to the Skull and Certain Ocular Findings". Dr. Walsh, a former Canadian, is one of the leading eye physicians in the United States and is the author of a textbook in clinical neuro-ophthalmology widely used all over the world. The Lectureship was established a year ago in honour of Dr. Wright who is Professor Emeritus of Ophthalmology.

Dr. Alan Parkin has been elected vice-president of the Canadian Psychoanalytic Society. In July he read a paper on "Fetishism" to the British Psychoanalytic Society. In October he read another paper on "Some Influences of Primary Identification" to the Canadian Psychoanalytic Society in Montreal.

Dr. Norma Ford Walker spent the first part of June in Trinidad studying children of mixed racial origin as part of the research program for the Hospital for Sick Children. Dr. Walker was an invited speaker at three meetings: International Association for Identification in Pittsburgh; IX International Congress of Pediatrics in Montreal; and Canadian Association for Retarded Children in Charlottetown, P.E.I. Dr. Walker has been appointed to the Board of Trustees of the Queen Elizabeth II Canadian Fund to aid in research on the Diseases of Children.

Dr. Milton Brown presented a paper entitled "'A' Substance in Typhoid Vaccine" at the International Symposium of Immunology held at Apatija, Yugoslavia to celebrate the 65th anniversary of the Institutes of Immunology at Zagreb. Dr. Brown also gave a paper entitled "Recent Advances in Immunization" at the Hamilton Academy of Medicine Annual Clinical Day.

Dr. John Hastings was a panel member on "Challenge of the National Hospital Plan" at the Canadian Welfare Association conference in Ottawa, and participated in a panel on "The Impact of Hospital Insurance" at the Ontario Welfare Council Conference; he gave three lectures on "Public Health Administration in Canada" at the Course on Hospital Administration of the Canadian Hospital Association.



CIBA

Presents

"ON INSPECTION"

J. SCHATZKER, 6T0

J. J. KAZDAN, 6T0

FIGURE 1. The diagnosis stares you in the face! Or does it? What other signs and symptoms might you find?



FIGURE 2. What is the name of this sign? In what conditions may you find this sign present?

Answers to "On
Inspection" may be
found on page 135



FIGURE 3. Do you see anything abnormal?



FIGURE 4. What is the name of the procedure carried out? When would you advise it?

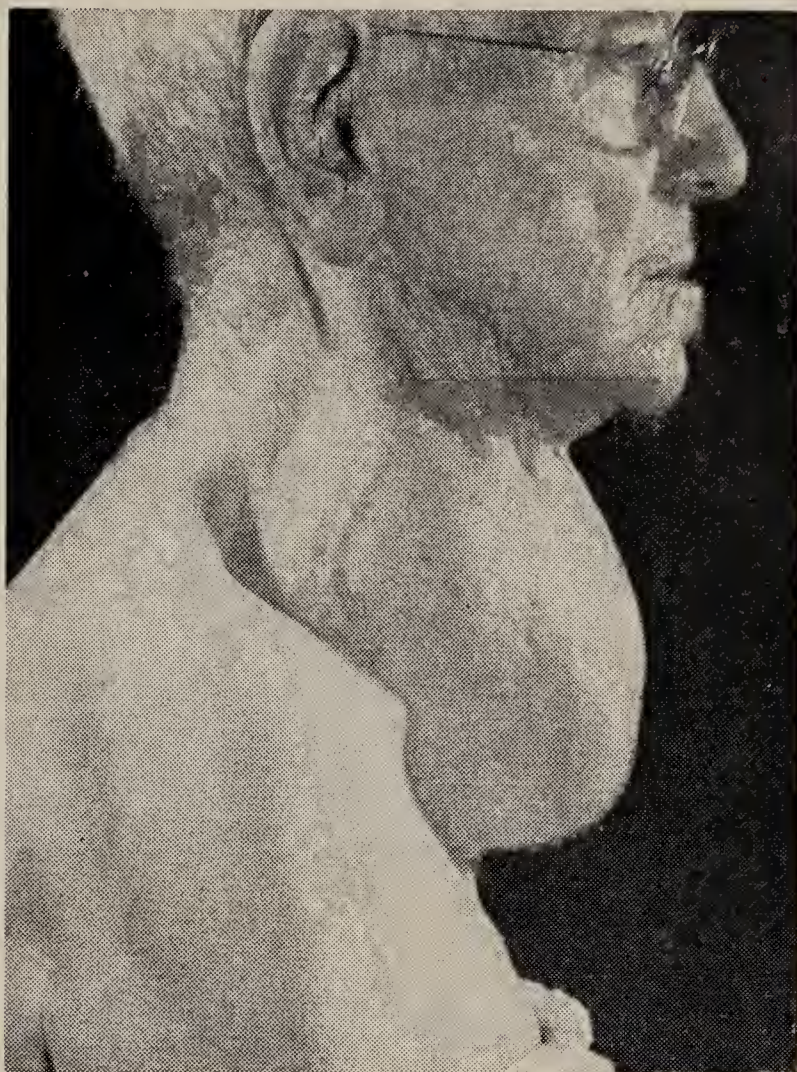


FIGURE 5. What is the most likely diagnosis? Give a differential diagnosis of lumps in the neck.



FIGURE 6. While bathing the patient noticed a painless swelling of his right testicle. What is your diagnosis? Give a differential diagnosis and some of the tests you would do.

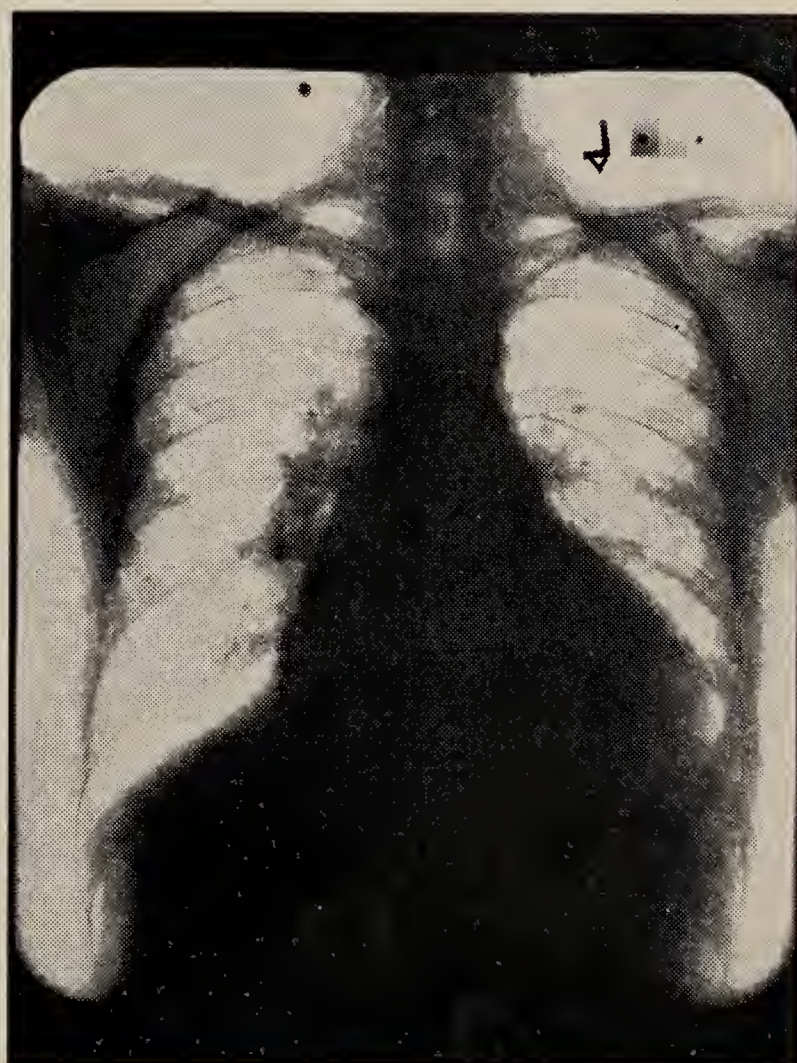


FIGURE 7. This 29-year-old man presented with paroxysmal nocturnal dyspnea. By careful scrutiny of the X-ray you can make the diagnosis. How would you confirm it clinically?

Good, although classification is
rather massive

DIFFERENTIAL DIAGNOSIS OF SPONTANEOUS GENERALIZED BLEEDING

PETER ADAM, 6TO

THE purpose of this article is to discuss the differentiation of diseases in which bleeding at any site may be the presenting symptom. Rather than emphasizing common disorders, I shall try to provide the necessary framework of classification, and an approach to the problem case through history, physical and special examinations. Of necessity, the article will deal with the physiology and laboratory testing of coagulation defects, and thus excludes a thorough discussion of other disorders.

CLASSIFICATION

The classification is a clinical one, based upon the method of investigation and thus, the principal areas in which a deficiency may lead to a bleeding tendency. Deficiencies occur (1) in the vessels and the tissues around the vessels, (2) in the clotting mechanism (which includes platelet factors) and (3) in the platelets themselves. Laboratory investigation in an orderly fashion will pinpoint the type of defect, and finally, the deficiency itself.

Table I: DIFFERENTIAL DIAGNOSIS OF
BLEEDING

I Vascular Abnormalities

- (A) Injury to large and medium sized vessels: trauma, other pathological processes leading to erosion.
- (B) Small vessel and capillary pathology:
 - (1) Congenital: hereditary hemorrhagic telangiectasia, von Willebrand's disease (pseudohemophilia), orthostatic purpura.
 - (2) Physical and chemical agents: trauma, mechanical purpura, increased hydrostatic pressure, snake venoms, bacterial toxins (scarlet fever).
 - (3) Infections: streptococcal, sta-

phylococcal, pneumococcal and meningococcal septicemia; measles, chronic debilitating diseases.

- (4) Intravascular: hypoxia, polycythemia, thrombocytopenic purpuras.
- (5) Metabolic: scurvy, uremia, diabetes.
- (6) Allergic: Henoch-Schönlein purpura, specific allergic purpuras, anaphylactoid, purpura simplex (multiforme, bullosum, vesiculatum, nodosum).

(C) Extravascular:

- (1) Atrophy of subcutaneous tissues: purpura senilis and cachectica.
- (2) Fragility or hyperlaxity of skin: Cushing's syndrome, Ehlers-Danlos syndrome, epidermolysis bullosa.
- (3) Dysglobulinemias: Cryoglobulinemia, macroglobulinemias, purpura hyperglobulinemia, multiple myeloma.

II Platelet abnormalities

A. Quantity:

- (1) Idiopathic thrombocytopenic purpura.
- (2) Symptomatic thrombocytopenic purpura.
 - (i) Chemical and physical agents:
 - (a) Chemical myelosuppressive drugs: nitrogen mustard, TEM, myleran, urethane, 6-mercaptopurine, aminopterin.
plus: oris root, snake venom, pertussis vaccine.
 - (b) Sensitivity to drugs: arsenicals, quinidine, quinine, sulphonamide, heavy metals (gold), phenyl butazone, antibiotics (aureomycin, chlorampheni-

col), tridione, organic hair dyes, DDT, estrogen.

(c) Physical: X-ray, heat stroke, burns.

(ii) Infections: septicemia, sub-acute bacterial endocarditis, typhus, measles, vaccinia, chicken pox, infectious mononucleosis.

(iii) Blood disorders:

(a) Leukemias.

(b) Anemias: aplastic, myelophthisic, pernicious anemia, acquired hemolytic anemia.

(iv) Splenic: congestive splenomegaly, leukemias, congenital hemolytic anemias, Gaucher's disease, Hodgkin's disease.

(v) Circulating anti-platelet globulins: Hodgkin's disease, leukemia, collagen diseases, multiple myeloma, sarcoidosis.

(vi) Massive blood transfusion.

(vii) Thrombotic thrombocytopenic purpura (acute purpura with platelet thrombi in capillaries).

B. Quality:

Thrombocytopathia:

Glanzmann's thrombasthenia.

III. Deficiencies of Clotting Mechanisms

(A) Phase I (thromboplastin) deficiency:

(1) Anti-hemophilic globulin (AHG) deficiency (hemophilia).

(2) Plasma thromboplastic component (PTC) deficiency (Christmas disease).

(3) Plasma thromboplastic antecedent (PTA) deficiency.

(4) Platelet thromboplastic factor deficiency (Glanzmann's thrombasthenia).

(B) Phase II (prothrombin complex) deficiency:

(1) Prothrombin and factor VII deficiency.

(i) congenital.

(ii) dicoumarol and salicylate intoxication.

(iii) lack of vitamin K: obstructive

jaundice, biliary fistula, impaired intestinal absorption, impaired bacterial growth in intestine, hemorrhagic disease of newborn.

(iv) severe liver disease.

(2) Factor V deficiency (parahemophilia).

(i) congenital.

(ii) acquired: liver disease, leukemia, pernicious anemia, exchange transfusions.

(iii) Stuart-Power factor.

(C) Phase III (fibrinogen) deficiency.

(1) congenital.

(2) secondary: liver disease, disorders of bone marrow, accidents of labour (amniotic fluid embolism, retained dead fetus, abruptio placenta).

(3) proteolytic enzymes: fibrinolytic purpura due to shock, irradiation, burns, transfusion reactions.

(D) Circulating anticoagulants:

(1) dicoumarol, heparin.

(2) heparinoid, anaphylactic and peptone shock, irradiation, burns.

(3) hirudin.

(4) idiopathic.

IV Mixed clotting and vessel abnormality (vascular hemophilia).

The classification, as it stands, includes most of the disorders which cause either generalized or local bleeding. It is, however, important to realize that disease characterized by widespread vessel pathology or coagulation defect may present as bleeding at any site; and that the source of bleeding fails to characterize the disease. In children and infants mild coagulation defects often become manifest for the first time at sites of surgical interference (tonsillectomy, dental extraction, circumcision). Thus, local causes of bleeding must be eliminated in the differentiation of generalized bleeding. A simple regional classification of common causes of local bleeding is

included, therefore, but the historical, physical, and laboratory implications are left to the imagination of the reader.

Table 2: COMMON CAUSES OF SPONTANEOUS LOCAL BLEEDING

- (1) Nervous System: hypertension, arteriosclerosis, congenital aneurysm.
- (2) Ears, nose, throat: local irritation by mechanical and inflammatory processes, hypertension, skull fracture, fibroepithelioma.
- (3) Lungs: mitral stenosis, tuberculosis, abscess, bronchiectasis, tumour.
- (4) Gastrointestinal: peptic ulcer, oesophageal varices, carcinoma, ulcerative colitis, haemorrhoids.
- (5) Urinary tract: glomerulonephritis, stone, tuberculosis, tumour, polycystic disease.
- (6) Genital apparatus: uterine fibroids, ruptured ectopic pregnancy, functional bleeding, tumour.

HISTORY AND PHYSICAL EXAMINATION

This section will serve to illustrate the importance of history and physical examination. Many of the important differential points will be discussed under the specific defects.

HISTORY

The importance of good history-taking in bleeding disorders is its major part in etiological surveys. For example, family history may reveal a bleeding diathesis when hemorrhagic disease presents in childhood. Maternal health and medications may suggest the etiology of bleeding in the newborn. Sensitivity to drugs, biological materials and occupational and household chemicals, discovered by a careful history, may also point to probable causative factors. Recent evidence of measles, chickenpox or vaccination uncovers the post-infectious thrombocytopenic purpuras, and in children, feeding history may rule out vitamin deficiency as a likely cause of bleeding.

In certain cases, history may be the final diagnostic criterion. A good example

is Henoch's purpura in which a classical history may be decisive.

PHYSICAL EXAMINATION

Physical examination, like history, may be the diagnostic criterion. In hereditary hemorrhagic telangiectasia careful scrutiny of the skin and mucous membranes will reveal both the site and the cause of bleeding. During the examination, a particular attempt is also made to find signs suggestive of leukemia. Adenopathy, sternal tenderness, anemia out of proportion to blood loss, palpable spleen and liver may signify this dyscrasia. Extreme toxicity suggests the necessity of blood culture.

PHYSIOLOGY OF CLOTTING

To understand the physiology of clotting in its simplest form is to understand the laboratory investigation. The characteristics of each member of the cycle are now presented, both for diagnostic and therapeutic importance. The scheme is simple and concentrates on those factors which produce clinical entities by their lack.

The clotting mechanism is best organized as a three-phase process. In phase I *thromboplastic* activity is created in plasma, or tissue thromboplastin is released by traumatized cells. Thromboplastin then acts upon *prothrombin* in the presence of other factors, to produce *thrombin*, thus completing phase II. The third and final stage is the enzymatic alteration of circulating *fibrinogen* by thrombin to produce *fibrin* which weaves its reparative mesh on a base of platelets. Calcium is essential to the rapid progress of all phases.

PHASE I

The initiating factor is trauma to tissue, or to a vessel. In vessel trauma, platelets are deposited in the wound releasing plasma thromboplastic factor and the clotting cycle is started.

The important circulating plasma factors are as follows: anti-hemophilic globulin, plasma thromboplastic com-

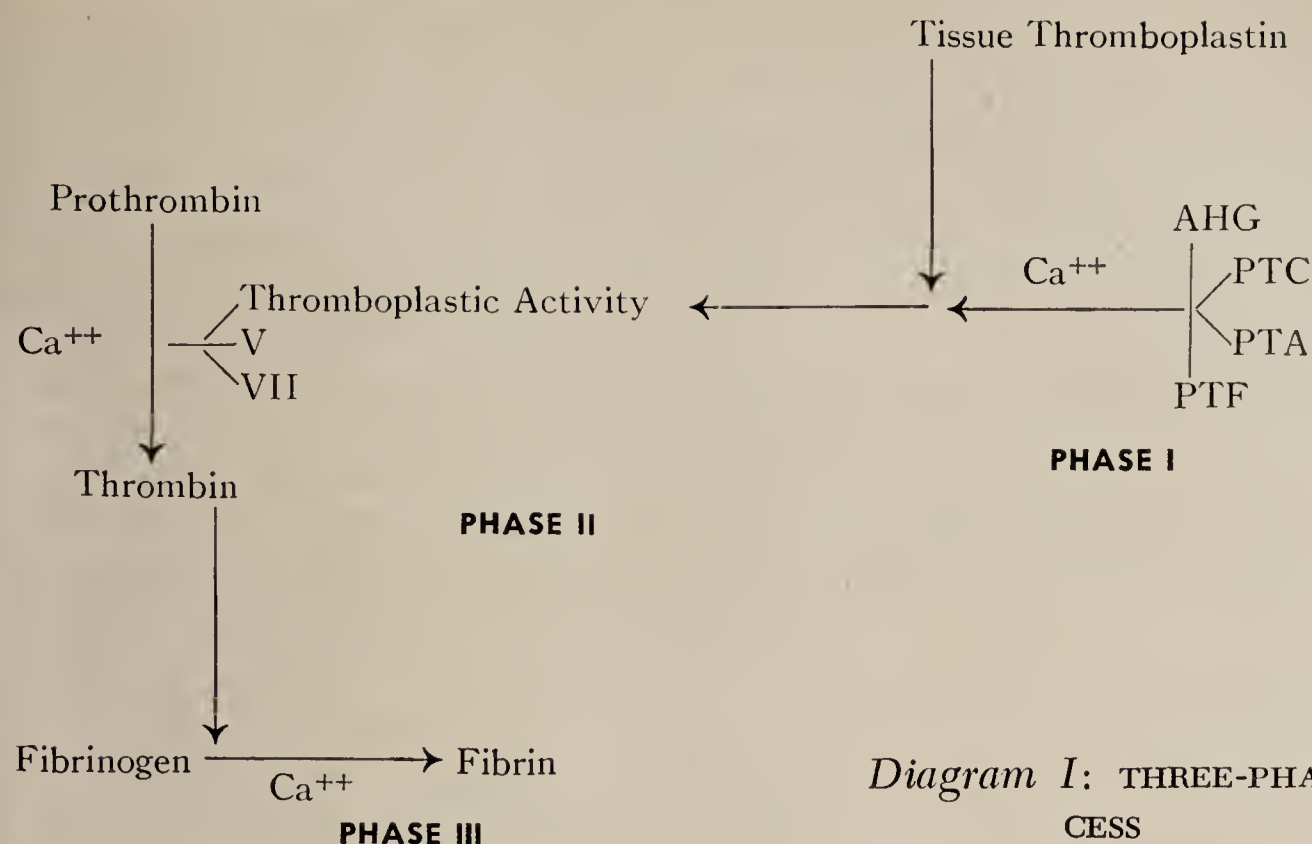


Diagram I: THREE-PHASE CLOTTING PROCESS

ponent, and plasma thromboplastic antecedent (AHG, PTC, and PTA). Of these, the AHG is labile and used completely in the clotting process *in vitro*, whereas PTC and PTA are stable on storage and not consumed during coagulation. The interaction of AHG, PTC, PTA and platelet thromboplastic factor in the presence of calcium produces thromboplastic activity.

PHASE II

Prothrombin in the presence of calcium and thromboplastic activity, and other circulating proteins—namely, factor V (proaccelerin) and factor VII (proconvertin)—is converted to thrombin, the catalyst of the final phase. Factor V is labile and completely consumed in clotting; factor VII stable and not consumed. Prothrombin is stable but is consumed in excess of seventy-five per cent during the normal clotting process.

PHASE III

This is the conversion of circulating fibrinogen to a fibrin precipitate in the presence of the thrombin and calcium. Fibrinogen is stable, but completely converted to fibrin in the normal coagulation process, and is thus not present in serum.

In addition to the above factors, physiological plasma anticoagulant factors are present in serum. The most important of these, clinically, is the plas-

minogen $\rightleftharpoons$ plasmin system, which is fibrinolytic. Fibrinolysokinase catalyzes the reaction, and antifibrinolysin inactivates the plasmin. In certain rare instances this system is activated by the products of destruction of tissue. Prostate, lung, and pancreas have peculiar ability to initiate activity in the proteolytic system. There are also anti-thromboplastic and anti-thrombin systems, acting to prevent thrombosis of the vascular tree.

MATERIAL USED IN LABORATORY INVESTIGATION

The plasma extracts used in the determination of defective coagulation are not pure preparations of the various factors, but are mixtures. They are easily prepared and available to any laboratory. The diagnostic materials are presented below, so that the principles of their use may be understood, but the procedures of standardization are omitted.

(1) *Plasma*: standardized collections of all the coagulation factors with sodium oxalate as the anticoagulant (takes calcium out of solution). With storage, there is loss of AHG and of factor V.

(2) *Serum*: During clotting AHG, factor V, prothrombin and fibrinogen are consumed, leaving PTC, PTA and factor VII in solution.

- (3) *Adsorbed plasma* (de-prothrombinized): Plasma may be adsorbed onto tricalcium phosphate gel, or onto barium sulphate. This process removes prothrombin, factor VII, PTC and some of the PTA. It leaves behind AHG, PTA, factor V and fibrinogen.
- (4) *Platelet suspension*: platelets are re-suspended in saline, after collection in siliconed bottles, and centrifuging.
- (5) *Calcium chloride solution* (0.25M) This solution is added to test solution to initiate clotting.

TABLE III
TABLE OF MATERIALS

Materials	Clotting Factors		
	I	II	III
Normal plasma	AHG PTC PTA	Prothrombin V VII	Fibrinogen
Stored plasma	PTC PTA	VII	Fibrinogen
Serum	PTC PTA	VII	—
Adsorbed plasma	AHG PTA	V	Fibrinogen

LABORATORY INVESTIGATION

Laboratory investigation proceeds in an orderly fashion. No one test is diagnostic but depends for its meaning upon other tests. The investigation will be discussed under the following headings:

- (1) Routine tests to establish a coagulation defect
- (2) Identification of phase
- (3) Determination of specific deficiency
- (4) Vascular factors
- (5) Detection of circulatory anticoagulant

As will be seen, certain of the specific deficiencies will be established early by this scheme of investigation, and they will be described as they are differentiated.

(1) ROUTINE TESTS

The screening tests first establish that

there is a bleeding defect, and secondly often suggest the sort of investigation required for its elucidation. Included are the bleeding time, coagulation time, clot retraction, capillary fragility, smear and differential, and platelet counts. As can be seen in Table IV, the tests are diagnostic in only one instance—platelet deficiency. Abnormal bleeding time, clot retraction, and tourniquet tests, with normal clotting time and low platelet counts (checked by smear) are diagnostic. Abnormal bleeding time and a positive tourniquet test are highly suggestive of capillary or platelet pathology, and prolonged clotting time, highly suggestive of coagulation defects. But none of these tests is absolute.

Included in the early investigation of any bleeding disorder are smear and differential. These are especially important in ruling out leukemias, which commonly present with bleeding. Marrow puncture and lymph node biopsy are likewise indicated in suspicious cases of undetermined etiology. Smear may also turn up atypical lymphocytes, which will add the Paul-Bunnell test to the battery of tests.

It has already been stated that the routine tests are not always reliable indicators of the type of disorder. They may also be misleading by dint of their inadequate sensitivity. The routine tests will *not* rule out a coagulation defect. History of recurrent bleeding, with no local cause is, therefore, indication enough for an extensive investigation. Some minimal disorders will only be discovered by the most sensitive of these specific tests, such as thromboplastin generation test.

Thrombocytopenic purpura

An investigation that has proceeded this far is adequate, as stated before, to diagnose thrombocytopenic purpura. A useful addition, bone marrow puncture, will reveal abnormal megakaryocytes.

Thrombocytopenic purpura may be either idiopathic or symptomatic. The idiopathic form is an acquired disorder

TABLE IV
SCREENING TESTS

Disorder	Bleeding Time	Clotting Time	Clot Retraction	Capillary Fragility	Platelet Count
Platelets: Thrombocytopenia	A	N	A	A	A
Thrombasthenia					N
Thromboplastin: AHG PTC PTA	N	A _(N)	N	N	N
Prothrombin: Prothrombin V VII	N or A	N or A	N	N or A	N
Fibrinogen:	N	A	N	N or A	N
Capillaries:	N or A	N	N	N or A	N

N = Normal; A = Abnormal; A_(N) = Normal in minimal deficiency.

usually occurring in children and young adults, mainly female. To diagnose it the clinician must rule out the causative factors of the symptomatic forms. Drugs may cause symptoms by a sensitivity mechanism, in which isoagglutinins are produced against platelets and their precursor in marrow. Among the important drugs are sulpha, quinine, quinidine, gold and phenyl butazone. Infectious processes such as the septicemias or subacute bacterial endocarditis will be suggested by history of exposure, severe constitutional reactions and blood culture. In paediatric practice, purpura occurs five to fourteen days following virus infections (measles, vaccinia and chicken pox). Infectious mononucleosis may also present as a bleeding disorder of this type. Of the blood dyscrasias the leukemias are diagnosed by peripheral smear and marrow puncture, as are aplastic, myelophthisic, and pernicious anemias. Treatment with the myelo-suppressive drugs also contributes to the platelet deficiency. Acquired hemolytic anemia is suggested by history of associated jaundice and anemia, typical disturbances in bile pigment metabolism and a positive Coomb's test.

With these factors eliminated, diagnosis of idiopathic thrombocytopenic purpura will stand.

(2) IDENTIFICATION OF PHASE

This next essential in the identification of a bleeding disease is done in reverse order; that is, phases III, II and I are eliminated respectively. This sequence is made necessary since, in deficiency of fibrinogen, there is prolongation of prothrombin time, and, with deficiencies of the prothrombin complex, there is an increased serum prothrombin time (which is the measure of thromboplastic factors).

Phase III

Abnormalities of fibrinogen concentration may be discovered by one of two tests.

(1) Semi-quantitative:

Commercial human thrombin, in excess, is added to patient's and to a control blood sample. The clotting time, so determined, is prolonged in fibrinogen deficiency.

(2) Plasma fibrinogen concentration:

Fibrin is precipitated on a moving glass rod, and nitrogen content determined by micro-Kjeldahl.

Afibrinogenemia and hypofibrinogenemia are rare causes of bleeding. A congenital form has been described and is due to deficient fibrinogen formation. In

accidents of labour (amniotic fluid embolism, retained fetus, abruptio placenta) thromboplastin may enter the maternal circulation through endometrial venous tears in high concentrations with resultant defibrinogenation by extensive intravascular capillary thrombosis. Abnormal proteolytic activity (fibrinolytic purpura) occurs during operations on the pancreas and prostate, shock, transfusion reactions, severe burns, anaphylactoid reactions and in association with carcinoma of the prostate or pancreas. These purpuras are apparently due to activation of plasminogen and its conversion to plasmin. Acquired afibrinogenemia has also been described in severe liver damage (acute yellow atrophy), disseminated malignant disease (especially of bone marrow), leukemia, polycythemia rubra vera, scurvy and pellagra. A low fibrinogen level in liver disease is due to decreased production and is a terminal event.

Phase II

Quick's one-stage prothrombin time is used to determine deficiencies of prothrombin and factors V and VII. An excess of calcium chloride and commercial thromboplastin is added to the patient's plasma, the time required for coagulation being measured from the moment of addition of thromboplastin. The test should be compared with a normal (12–14 seconds). Since all the thromboplastic factors are accounted for, this test will reveal deficiencies of (1) the prothrombin complex and (2) fibrinogen, and is, therefore, only valuable in estimating phase II if the concentration of fibrinogen has already been determined.

Phase I

There are two tests available to the clinician in search for reduced thromboplastic activity.

(1) Prothrombin consumption test

This method is based upon the principle that the amount of prothrombin utilized during clotting is a measure of thromboplastic activity, that is, the

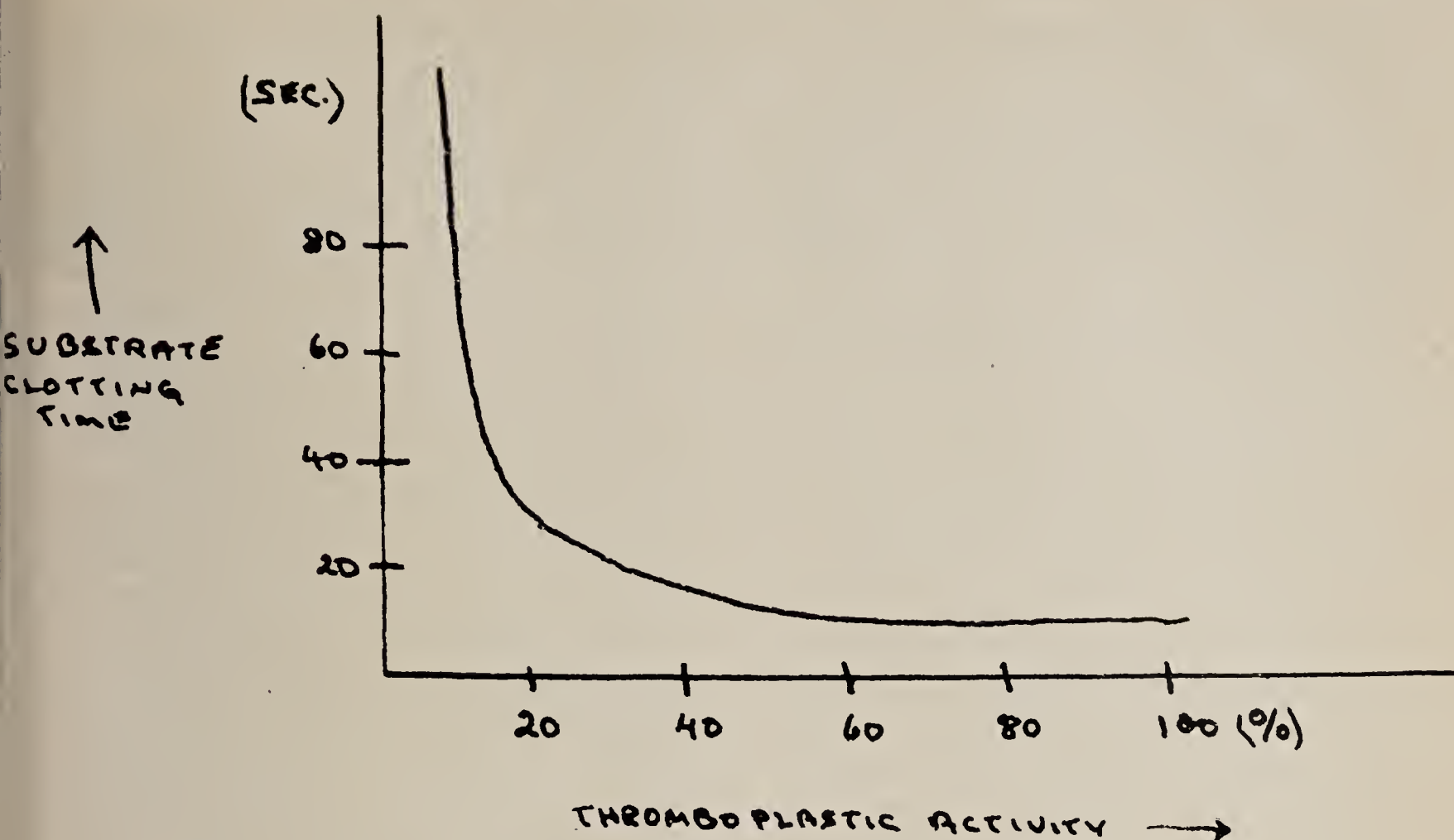
capacity of plasma to generate thromboplastin from AHG, PTC, PTA and platelet thromboplastic factor (PTF). The patient's blood is allowed to clot (1 hour) and the serum withdrawn. In so doing not only prothrombin is consumed (75% in the normal) but also AHG and labile factor are destroyed. Adsorbed plasma is added to replace labile factor V, and a "serum prothrombin time" is done; i.e. thromboplastin and calcium chloride are added to the mixture as in Quick's one-stage method. Normally serum prothrombin time is greater than twenty-five seconds. In cases of severe deficiency of a thromboplastic factor, the serum prothrombin time may be as low as twelve to fourteen seconds.

(2) Thromboplastin generation test (TGT)

This is complicated, but is the most sensitive method of determining the activity of the first phase in the clotting mechanism. It involves the construction of a standard curve of thromboplastic activity as follows:

De-prothrombinized plasma (AHG), serum (PTC and PTA), platelet suspension and calcium chloride from a normal person are incubated at 37 degrees centigrade, and aliquots taken at 1, 3, 5, 7 etc. minutes. The aliquots are then added to a substrate of normal platelet-free plasma. To add to these samples is to add already "activated" thromboplastin to normal plasma; i.e. as in a prothrombin time. Normally, a minimum clotting time (i.e. maximum thromboplastin activity) of 8–10 seconds is reached after 3–7 minutes of incubation. This time (8–10 seconds) is equated with 100% thromboplastic activity. By serial dilution of incubation mixtures and addition of diluted aliquots to substrate plasma, a standard curve is created. Thus, the clotting time of substrate plasma may be expressed in terms of thromboplastic activity (percent of normal).

Now, mixtures of adsorbed plasma and serum from the patient mixed with normal platelets may be incubated as above. Aliquots will behave like the



STANDARD CURVE OF THROMBOPLASTIC ACTIVITY

diluted samples of the standard curve and activity measured by comparison with it. The activities at 1, 3, 5, 7 etc. minutes are plotted till maximum activity is reached. A normal TGT is at least 90%.

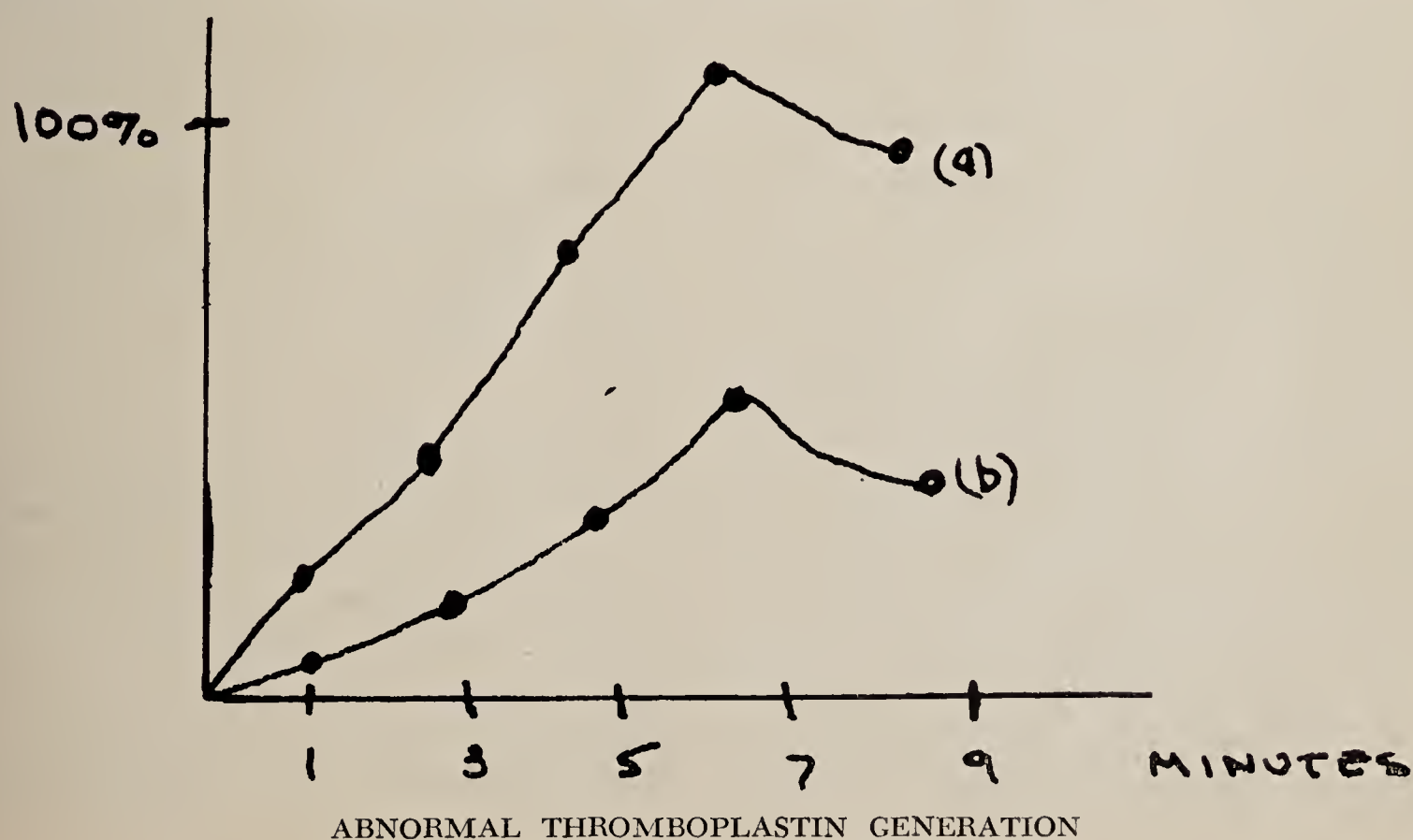
- (a) maximal activity in normal
- (b) maximal activity in 40% thromboplastin generation. (i.e. minimum clotting time of a bit less than 20 seconds).

There are two important differences

between the above tests:

(1) TGT is more sensitive than prothrombin consumption tests.

(2) Prothrombin consumption depends upon normal prothrombin activity in the patient's serum, whereas TGT does not. As in the previous tests, therefore, the integrity of the phases which follow (both II and III) must be proven before prothrombin consumption test can be interpreted.



(3) DETERMINATION OF SPECIFIC DEFICIENCIES

This aspect of differentiation concerns only phases I and II. In the application of laboratory procedures for specific determinations, one of two principles may be used:

(1) Determination of which factor by its addition will return a phase-specific test to normal.

(2) Determination of the defect by having all coagulation factors present in excess, except the one being tested. By this method, the patient's plasma is added to a standard sample which is known by previous testing to be deficient in a certain factor. Although the principles of these tests are simple enough, their practice is not. The first method is complicated by the absence of pure coagulation factors; the second, by its requirement for a battery of factor-deficient plasmas from known patients. Both methods require rigid controls to allow for the various dilutions which take place as solutions are added to test mixtures. Reference to *Advances in Pediatrics* will supply comprehensive examples of method.¹

Phase II

Once the phase has been determined, specific lack may be pinpointed easily by addition of the sample materials discussed earlier to the abnormal one-stage prothrombin time. Adsorbed plasma will correct the prothrombin time of factor V deficiency: serum will correct it in factor VII lack, and neither will correct it in prothrombin deficiency.

Congenital deficiencies of phase II components are rare. Most common is congenital lack of factor VII which, like other prothrombin deficiencies is inherited as a Mendelian dominant and affects both sexes. Included with the deficiency of factor VII is the newly described Stuart-Power factor, an incompletely recessive autosomal characteristic. Of the familial phase II deficiencies, hypoprothrombinemia is the rarest. Con-

genital factor V deficiency or parahemophilia is less rare.

Clinically, acquired deficiencies of prothrombin and factor VII are closely related. Principal hepatotoxins reducing prothrombin and factor VII levels in blood are salicylates and derivatives of dicoumarol. Lack of vitamin K, with its multiple pathogenesis, likewise contributes to the host of hypoprothrombinemias. Since bile salts are needed for the absorption of this fat soluble vitamin, biliary obstruction or fistula may cause vitamin K deficiency. The same situation occurs with bowel malabsorptions associated with the steatorrheas, gastrocolic fistulas and surgical removal of large portions of bowel. Broad spectrum antibiotics may eliminate the coliform organisms responsible for the production of vitamin K and likewise cause prothrombin and factor VII deficiency. In the neonatal period, hemorrhagic disease of the newborn is caused by lack of vitamin K. The fetus and infant depend upon the prothrombin supply received from the mother transplacentally until, with the ingestion of food, bacteria begin to grow in the intestine.

Severe liver damage is another cause of decreased production of prothrombin and factor VII. It is, however, rarely a cause of bleeding. Combined deficiency of all clotting factors is, as suggested before, indicative of very severe parenchymal liver disease, and is usually terminal.

Labile factor is sometimes independently deficient in sepsis, leukemia and after exchange transfusions for erythroblastosis fetalis.

Phase I

Before launching the investigation of phase I, I should like to emphasize the importance of platelets in this phase. Usually the diagnosis of platelet lack is completed with the routine tests. When, however, the deficiency is one of platelet quality, rather than of quantity, it is the modification of the thromboplastin

generation test which clinches the diagnosis. Poor clot retraction in the presence of normal platelet count is highly suggestive.

The first principle of specific deficiency determination may be used at any level, depending upon the relative disturbances of clotting time, prothrombin time, prothrombin consumption or thromboplastin generation; that is, the effect of normal plasma, normal adsorbed plasma and normal serum upon any of these abnormal coagulation tests may be used in the differentiation, provided the disturbance of clotting varies adequately from the normal which is used as the control. As in tests differentiating phase II, controls must be treated in exactly the same way as tests, to allow for dilution. Below, in table V is a summary of the results expected in deficiency of AHG, PTC and PTA.

ADDITION OF SPECIFIC THROMBOPLASTINS TO CORRECT ABNORMAL CLOTTING TESTS IN THE DIFFERENTIATION OF PHASE I DEFICIENCIES.

TABLE V

Reagent	Adds	Deficiency		
		AHG	PTC	PTC
Normal plasma	All factors	+	+	+
Normal adsorbed plasma	AHG PTA	+	—	+
Normal serum	PTC PTA	—	+	+

If the clotting time of whole blood is too insensitive for the test, the other tests may be avoided by simply using the recalcification time of plasma. This is a very sensitive test. (Normal is 90–100 seconds after addition of CaCl_2 .)

MODIFIED THROMBOPLASTIN GENERATION TEST

Application of this test to the diagnosis of specific deficiency utilizes the second

principle of laboratory differentiation. All the clotting factors are present in the incubation mixtures except the factor suspected to be deficient in the patient's plasma. By the use of this sensitive test deficiencies of AHG, PTC, PTA and of platelet quality (Glanzmann's thrombasthenia) are differentiated. In the incubation mixture of adsorbed plasma, platelets and serum, the products of patient's plasma are substituted in turn as follows:

- (1) patient's adsorbed plasma
- (2) patient's serum
- (3) patient's adsorbed plasma and serum
- (4) patient's platelets
- (5) patient's adsorbed plasma, serum and platelets.

The alterations in thromboplastic activity are diagnostic (see table VI: DIFFERENTIATION OF PHASE I DEFICIENCY WITH THE MODIFIED THROMBOPLASTIN GENERATION TEST).

The important deficiencies of thromboplastic factors are congenital and familial. As a result, they often present in infancy or early childhood, although milder cases may not be discovered till an operation at a later age. Common presenting symptoms are bruising, epistaxis, hemarthrosis and bleeding or oozing with the loss of teeth. Circumcision, tonsillectomy or dental extraction may likewise initiate symptoms in a hemorrhagic diathesis. Hemophilia (AHG deficiency) and Christmas disease (PTC deficiency) are Mendelian recessives, sex-linked and occur only in males. (The daughter of a female carrier and a male hemophiliac may, however, be affected). Deficiency of PTA is inherited by a Mendelian dominant gene and occurs in both males and females.

Acquired deficiencies of thromboplastins are extremely rare. An antithromboplastin to AHG has been demonstrated after repeated transfusions or after pregnancy. Other antithromboplastins have been demonstrated in diseases like disseminated lupus erythematosus.

TABLE VI

Substitute	Deficiency			
	AHG	PTC	PTA	Platelets
Normal incubation mixture (control)	N	N	N	N
Patient's adsorbed plasma	(A)	N	N	N
Patient's serum	N	(A)	N	N
Patient's adsorbed plasma and serum	N	N	(A)	N
Patient's platelets	N	N	N	(A)
Patient's platelets, serum, adsorbed plasma	(A)	(A)	(A)	(A)

(4) VASCULAR FACTORS IN HEMORRHAGIC DISEASES

There are two groups of diseases characterized by vascular abnormalities.

- (i) Those in which the vascular abnormality is the only defect.
- (ii) Those in which functional and morphological capillary change is associated with a deficiency of a coagulation factor in the first group of disorders.

Hereditary hemorrhagic telangiectasia can easily be diagnosed on physical examination by the characteristic multiple capillary dilatations in skin and mucous membranes. Capillary microscopy of the nail beds is required to diagnose von Willebrand's disease. Both disorders are inherited as Mendelian dominants and present in both males and females. Constitutional capillary fragility is likewise contributory in orthostatic purpura, familial purpura simplex and familial epistaxis.

Among the acquired disorders, Henoch-Schönlein's purpura is a hemorrhagic disease characterized by bleeding into the skin, gastrointestinal tract, kidney, and joints. It is probably one of the group of allergic purpuras which are initiated by an unknown hypersensitivity reaction. Other allergic purpuras may be characterized by history of exposure to sensitizing drugs, foods or contactants, bleeding into skin, joints and viscera, and other manifestations of allergy such as ery-

thema, urticaria, itching and effusions of serum into skin.

A large group of the so-called symptomatic purpuras are likewise characterized by capillary fragility and no demonstrable coagulation defect. Of the infectious processes, septicemias, virus disorders and chronic debilitating diseases must be thought of in the patient who is very ill. Chemical factors (snake venom) and physical agents (trauma, mechanical purpura with whooping cough, hydrostatic pressure) cause direct vessel injury. Scurvy, uremia, diabetes and Cushing's syndrome are the important metabolic disorders in which capillary function may be altered.

In the second group of vessel disorders which are characterized by a capillary malfunction plus a clotting defect, AHG deficiency is the most common among the familial disorders. This vascular hemophilia occurs in the spectrum between von Willebrand's pseudohemophilia and AHG deficiency. It is inherited by a Mendelian dominant present in both sexes.

(5) DETECTION OF CIRCULATING ANTI-COAGULANT

This is a technique which need rarely be used. Anticoagulants are normally present in blood to prevent total intravascular thrombosis. When blood levels are up, however, they may cause a

TABLE VII

Genetic Disorder	Sex	Gene
Hemophilia Christmas disease	Male	Sex-linked dominant
PTA Prothrombin Factor VII	Both	Dominant
Factor V Fibrinogen	Both	Partial dominant
Vascular hemophilia Pseudohemophilia	Both	Dominant

hemorrhagic diathesis. Detection depends on the ability of normal plasma to correct all clotting deficiencies in which there is *no* active anticoagulant. If normal plasma will not correct the recalcification time of a patient's plasma over a wide range of dilutions, then an active anticoagulant is assumed to be present.

SUMMARY

To reiterate the purpose of this article, it is meant as an aid to the differential diagnosis of generalized bleeding. As is fit for students of medicine, it copies the precepts and order of a "green-book" clinician. History is presented as an etiological survey and physical examination as a method to eliminate local causes of bleeding. History and physical are, in the same moment, visualized as the guiding lights of laboratory investigation. Laboratory methods narrow the field to a specific deficiency, and the aspirant to diagnosis performs the final step, by coordinating the laboratory findings with the history and physical examination.

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C-REACTIVE PROTEIN

A positive test indicates an acute stage of an inflammatory or necrotizing process. This test is a valuable adjunct in the establishment of the diagnosis of rheumatic fever, rheumatoid arthritis, subacute bacterial endocarditis and in distinguishing malignancy from inflammatory disease. It is also found in the blood of patients with staphylococcal osteomyelitis, pneumococcal pneumonia, tuberculosis and myocardial infarction, as well as in certain viral diseases.

Parke-Davis, Therapeutic Notes, Vol. 65, No. 2, Feb. 1958.

ABDOMINAL PAIN OF CEREBRAL ORIGIN

The author postulates two groups: the first consists of those with true abdominal migraine in which there is a family history of migraine and the E.E.G. is normal. The second includes those in which there is no family history of migraine; the attacks are of much shorter duration, are associated with confusion, nausea, vomiting or vasomotor symptoms and are accompanied by an abnormal E.E.G. They represent cases of true temporal lobe abdominal epilepsy. The importance of the distinction is to avoid alarming the parents and child by labelling the first of these as epilepsy.

J. S. Prichard, C.M.A.J. May 1, 1958.

ABSTRACTS

GRISEOFULVIN: A CLINICAL REPORT, W. D. Stewart, B. Kanee, J. L. Danto, S. W. Maddin, C.M.A.J., Nov. 1, 1959.

Griseofulvin is a metabolic product of several species of fungus, notably *Penicillium Griseofulvin*. It has shown antibiotic properties against fungal elements growing on plants, animals and man, that make it useful in clinical medicine as a therapeutic agent beneficial in superficial fungal infections.

Griseofulvin is given orally in tablet form and appears to become incorporated into the new skin, hair and nails, from which position it exerts its antifungal action. It is essentially fungistatic, providing an advancing barrier of fungus-resistant keratin rather than exerting a fungicidal effect upon those viable fungal elements already lodged in the keratinous structures. Griseofulvin appears to be a safe drug with low toxicity and few side effects in the therapeutic range. It brings into the range of successful therapy some fungal infections which have been considered virtually incurable.

The seven cases in this study were either untreated or unresponsive to all other treatment. All had proven laboratory evidence of fungal infection. Cases 1 and 2 were previously untreated cases of *Tinea capitis* due to *Microsporum canis* infection in children. Case 3 was a *Microsporum gypseum* infection involving nails and skin of at least seven years' duration in an adult. It had remained unaffected by standard topical antifungal agents and strong peeling preparations. The remaining four cases consisted of recalcitrant *Trichophyton rubrum* infections of adults, varying from 3 to 13 years in duration and resistant to all previous forms of local therapy.

All therapy was given orally, with no accompanying local treatment. Griseofulvin was given in dosages of 1 to 2.5 g. daily. Treatment was maintained for 6 to

26 weeks. Only the *Trichophyton gypseum* infection did not show a satisfactory clinical response, although the cultures became negative. It is quite possible, however, that the remaining lesions in the nails and skin in this case were of psoriatic or other aetiology.

E. J. H.

TREATMENT OF BLEEDING OESOPHAGEAL VARICES. M. J. Mackby J.A.M.A., Dec. 5, 1959.

Haemorrhage from oesophageal varices is probably a reflection of anatomically undeveloped retroperitoneal collateral vessels. The exact mechanism of bleeding is obscure and cannot be reproduced in experimental animals.

Diagnosis of bleeding from the upper gastrointestinal tract is important and may be misleading because of the high incidence of peptic ulcer in patients with cirrhosis. In the author's series twenty-five per cent of bleeding cirrhotic patients bled from a concomitant peptic ulcer or gastritis. The best diagnostic and therapeutic tool in emergency situations is the Sengstaken-Blakemore tube. This tube is passed through the nose and into the stomach, the gastric contents aspirated and the gastric balloon inflated. Strong traction is applied on the tube and maintained. The oesophageal balloon is inflated to a pressure of 35-45 mm Hg. A roentgenogram will confirm proper positioning. Traction is necessary to prevent the oesophageal balloon from herniating into the stomach and assists in controlling haemorrhage. If the stomach is lavaged and bleeding into it continues, then the haemorrhage is from a peptic ulcer or high gastric varices. Other diagnostic measures include B.S.P. determination, blood ammonia level determination, barium swallow, liver biopsy, and hepatic wedged pressure studies.

If the Sengstaken tube fails to control bleeding, emergency laparotomy and gastrostomy is indicated. Bleeding peptic ulcer and gastric or oesophageal varices can be controlled through such an incision.

If bleeding is controlled by use of the Sengstaken tube, the oesophageal balloon is deflated in 24 hours. If bleeding recurs, the balloon is reinflated, fresh whole blood is obtained and the patient is prepared for surgery. If, after another 24 hours of compression, on release of the bag the bleeding recurs, the patient is taken to surgery and, either through a transabdominal or transthoracic incision, the varices are ligated. Prolonged tamponade (i.e. beyond 48-72 hours) results in a bulky, oedematous, indurated oesophagus which responds poorly to any type of surgical manipulation. The

patient also requires constant nursing care.

The patient should undergo some definitive shunt construction after 3-6 weeks in hospital, depending on his condition. Emergency shunt is not advocated in the usual situations in the average hospital. Elective or urgent porto-caval end-to-side shunt is recommended for all patients who have had recurrent bleeding from proven oesophageal varices, who are not jaundiced and who show no signs of ammonia intoxication. Such patients should be brought to the optimum level of hepatic function prior to surgery. Spleno-renal shunt is recommended for all those patients with extrahepatic block who have a splenic vein over 1 cm. in diameter.

E. J. H.

ANSWERS TO "ON INSPECTION"

FIGURE 1.

This is a case of bilateral exophthalmos occurring in a person with hyperthyroidism. Eye signs, other than proptosis, which are also seen in this condition are:

1. Lid retraction
2. Lid lag (von Graefe's sign)
3. Inability to maintain convergence or failure of convergence (Mobius)
4. Infrequent blinking (Stellwag)
5. Failure to wrinkle brow on upward gaze (Joffroy)
6. Lateral nystagmus (Sainton)
7. Tremor of closed lid (Rosenbach)
8. Stare (Dalrymple)
9. Vascular congestion of the pericorneal regions (Topolanksi)
10. Difficulty in everting the upper eyelid (Gifford)

Hyperthyroidism may occur at any age, especially during puberty, pregnancy and the menopause. The disease is much more frequent in females (8:1). It is usually associated with a diffuse goitre free of nodules. It is rare in children and when it does occur in childhood the ocular manifestations are usually absent.

FIGURE 2.

This is Trousseau's sign. It is due to contraction of the forearm and hand muscles. The characteristic position assumed is determined by the relative

strength of the individual muscle groups. The sign demonstrates low ionized serum calcium levels.

One of the factors which determine nerve excitability is the calcium ion concentration in the serum. Low levels enhance nerve excitability and this effect is potentiated by ischemia. The cuff produces ischemia of the parts distal to its application and in the presence of low serum calcium levels will make latent tetany manifest itself.

Alkalemia and hypocalcemia produce clinical tetany. The former occurs with excessive ingestion of alkali, in profuse vomiting or continuous gastric suction (hypochloremic alkalosis) and with hyperventilation, as seen in acute anxiety states. The latter occurs in hypoparathyroidism, rickets, osteomalacia, after surgical removal of the parathyroid glands, acute hemorrhagic pancreatitis and in renal failure with phosphate retention.

FIGURE 3.

Note the fusiform swelling of the fingers. This is a case of juvenile rheumatoid arthritis, a rare disease in children, but occurring as early as eighteen months of age. You should suspect this condition when a child has a persistent low-grade fever, general ill health, loss of weight, fatigue, and vague pains in the limbs. Usually the onset is insidious, but may be acute, and is then easily confused with acute rheumatic fever.

FIGURE 4.

A tarsorrhaphy operation has been carried out here. A union of the lids by means of intermarginal adhesions is performed when the lids are to be closed either temporarily or permanently. . .

This procedure is indicated in lagophthalmos, especially in the exophthalmos of thyroid disease, and paralytic ectropion. Neuroparalytic keratitis is also an indication.

FIGURE 5.

This is a case of carcinoma of the thyroid occurring in a woman in her late seventies. The diffuse enlargement of the gland is not typical and could easily be confused with a thyrotoxic goitre. This picture is included to illustrate that carcinomas of the thyroid need not present as nodular enlargements of the thyroid gland.

In considering masses in the neck a classification by location is very useful:

I Single

A. Midline

1. Submental glands
2. Thyroglossal duct cyst
3. Adenoma of the thyroid isthmus
4. Ectopic thyroid tissue
5. Dermoid cyst
6. Goitre

B Lateral

1. Benign thyroid adenoma
2. Benign salivary gland tumour
3. Branchial cleft cyst

4. Cystic hygroma
5. Pharyngeal pouch
6. Carotid body tumour
7. Cervical rib
8. Inflammatory lesions: boils, tuberculosis, actinomycosis
9. Soft tissue tumour
10. Vagus neurofibroma

II Multiple (Lymph nodes)

1. Infections
 - (a) Specific: tuberculosis, syphilis, measles, diphtheria, acute pharyngitis and tonsillitis, infectious mononucleosis, etc.
 - (b) Non-specific: septicemia, reticulosis, etc.
2. Neoplasms
 - (a) Primary: lymphomas, lymphosarcomas and leukemias
 - (b) Secondary: nasopharynx, breast, lung, prostate, testis and gastrointestinal tract.

FIGURE 6.

This is a seminoma of the testis.

Differential diagnosis:

1. Congenital polyorchidism or fusion: ruled out on the basis of gradual enlargement appearing in adulthood.
2. Traumatic: Orchitis or torsion—the latter may be excluded on history.
3. Inflammatory:
 - (a) chronic non-specific epididymitis
 - (b) tuberculosis of the testis—prostate and seminal vesicles are usually involved and urine usually shows pus cells
 - (c) syphilitic orchitis—serology
4. Fluid-containing cysts:
 - hydrocoele—transilluminate
 - hematocoele—aspirate
 - spermatocoele—aspirate
5. Hernia—you cannot get above an indirect hernia!
6. Neoplastic
 - Seminoma
 - Embryoma
 - Chorionepithelioma
 - Embryonal carcinoma
 - Teratocarcinoma
 - Adult teratoma
 - Interstitial cell tumour
 - Sertoli cell tumour
 - Tumours of the testicular stroma

FIGURE 7.

You can make the diagnosis of coarctation of the aorta by observing the notching of the ribs produced by enlargement of the intercostal arteries which act as collateral vessels.

The diagnosis is confirmed clinically by the finding of hypertension in the upper limbs together with diminished or absent femoral artery pulsation.

This patient went into cardiac failure, which accounted for the paroxysmal nocturnal dyspnea.

This feature has been made possible by the CIBA company for whose continued interest in medical education we are extremely grateful—Editor.

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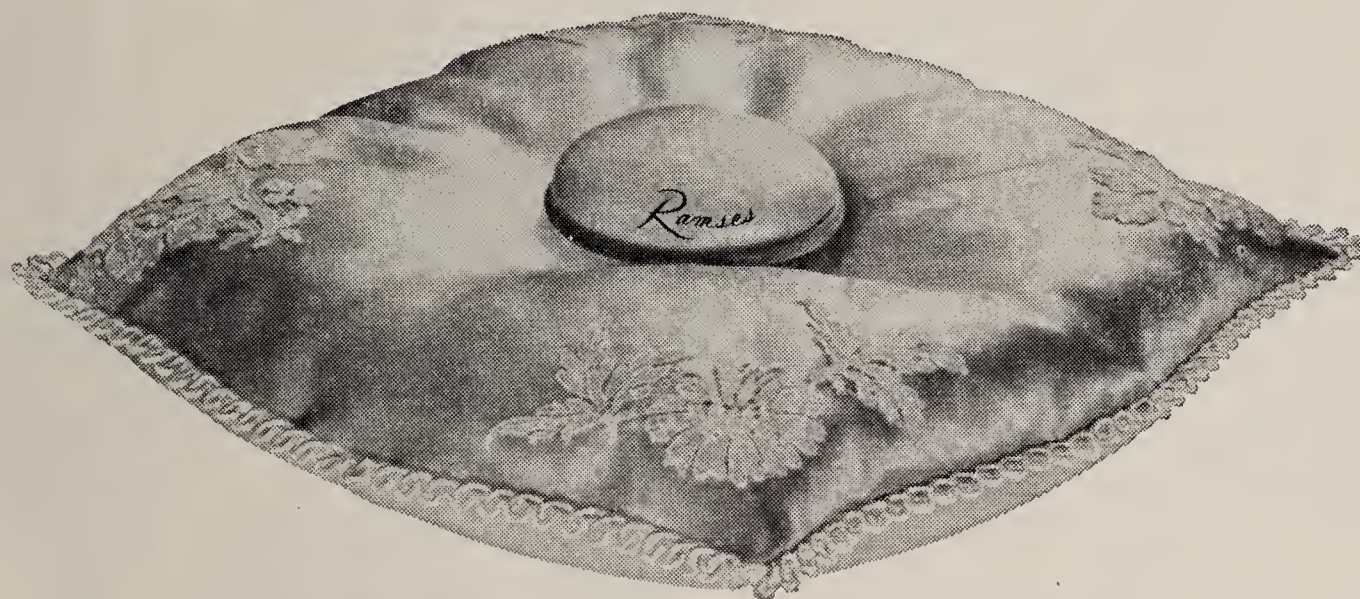
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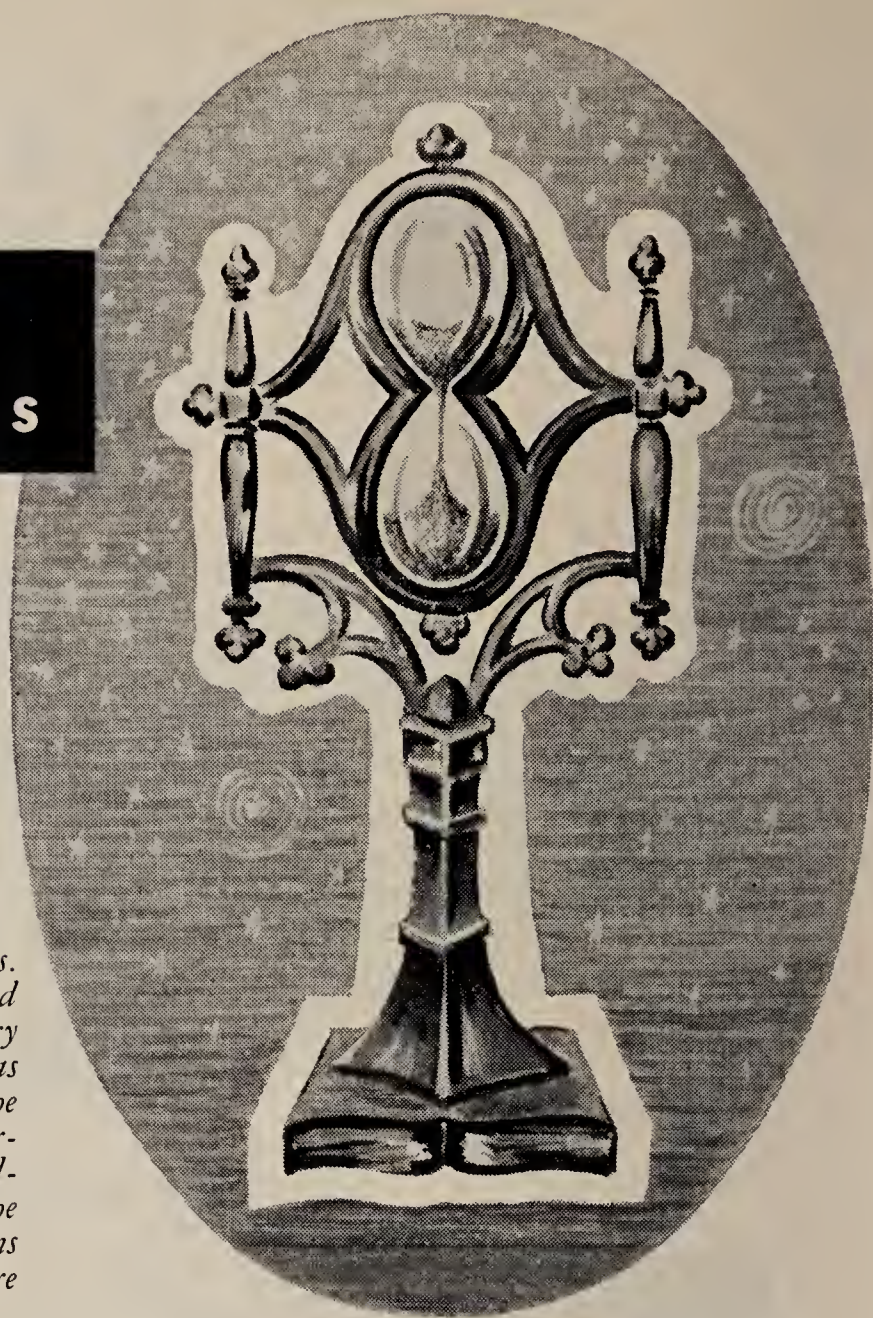
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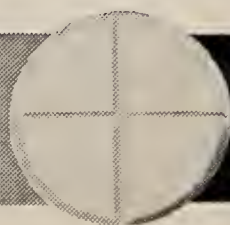
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